UNIT – I

Nomenclature of organic Compounds and Reaction Intermediates

Two Marks

1. Give IUPAC name for the compounds.
2. Write the stability of Carbocations.
3. What are Carbenes?
4. How Carbanions reacts? Give examples
5. Write the reactions of free radicals
6. How singlet and triplet carbenes react?
7. How arynes are formed?
8. What are Nitrenium ion?
9. Give the structure of carbenes and Nitrenes
10. Write the structure of carbocations and carbanions.
11. Give the generation of carbenes and nitrenes.
12. What are non-classical carbocations?
13. How free radicals are formed and give its generation?
14. What is [1,2] shift?

Five Marks

1. Explain the generation, Stability, Structure and reactivity of Nitrenes
2. Explain the generation, Stability, Structure and reactivity of Free Radicals
3. Write a short note on Non-Classical Carbocations.
4. Explain Fries rearrangement with mechanism.
5. Explain the reaction and mechanism of Sommelet-Hauser rearrangement.
6. Explain Favorskii rearrangement with mechanism.
7. Explain the mechanism of Hofmann rearrangement.

Ten Marks

1. Explain brefly about generation, Stability, Structure and reactivity of Carbocations
2. Explain the generation, Stability, Structure and reactivity of Carbenes in detailed
3. Explain the generation, Stability, Structure and reactivity of Carboanions.
4. Explain brefly the mechanism and reaction of [1,2] shift.
5. Explain the mechanism of the following rearrangements

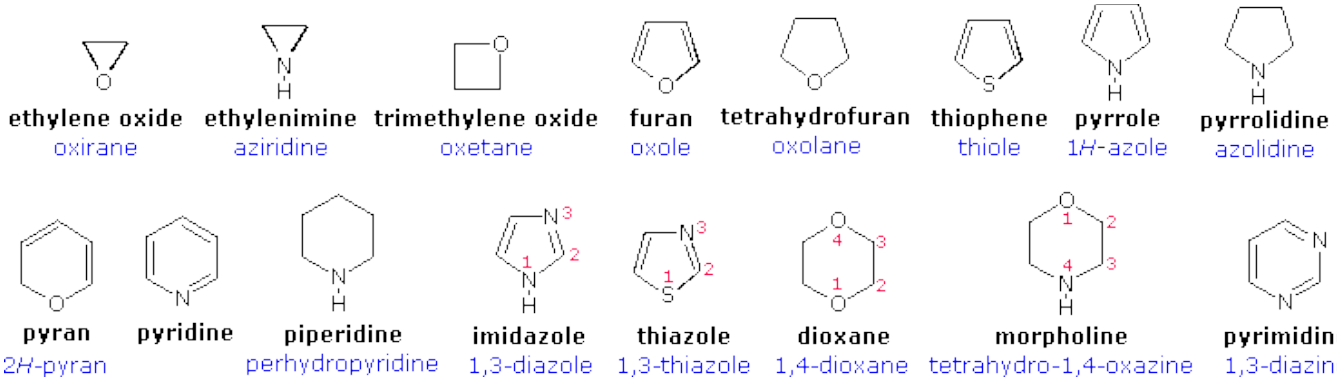
i) Wolf rearrangement ii) Stevens rearrangement iii) Benzidine rearragement

6. Explain the reaction and mechanism of Dienone-Phenol reaarangement in detailed
7. Explain the reaction and mechanism of Baeyer-Villiger rearrangement in detailed

Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, every carbocyclic compound, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulfur (the most common heterocyclic elements), the permutations and combinations of such a replacement are numerous.

Nomenclature

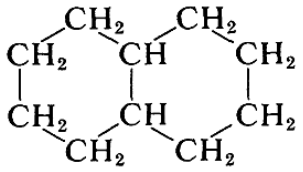
Devising a systematic nomenclature system for heterocyclic compounds presented a formidable challenge, which has not been uniformly concluded. Many heterocycles, especially amines, were identified early on, and received trivial names which are still preferred. Some monocyclic compounds of this kind are shown in the following chart, with the common (trivial) name in bold and a systematic name based on the Hantzsch-Widman system given beneath it in blue. The rules for using this system will be given later. For most students, learning these common names will provide an adequate nomenclature background.



An easy to remember, but limited, nomenclature system makes use of an elemental prefix for the heteroatom followed by the appropriate carbocyclic name. A short list of some common prefixes is given in the following table, priority order increasing from right to left. Examples of this nomenclature are: ethylene oxide = oxacyclopropane, furan = oxacyclopenta-2,4-diene, pyridine = azabenzene, and morpholine = 1-oxa-4-azacyclohexane.

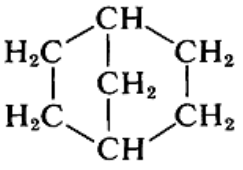
Nomenclature of alicyclic,bicyclic and tricyclic compounds

There are many hydrocarbons and hydrocarbon derivatives with two or more rings having common carbon atoms. Such a substance is decalin, which has ten carbons arranged in two six-membered rings:

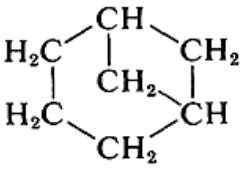


decalin
(bicyclo[4.4.0]decane)
(decahydronaphthalene)

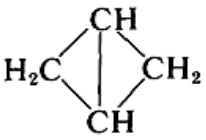
Compounds of this type usually are named by attaching the prefix *bicyclo* to the name of the open-chain hydrocarbon with the *same total number of carbon atoms as in the rings*. Thus decalin, which has ten carbons in the ring system, is a *bicyclodecane*. Next, we have to have a way to specify the sizes of the rings, which is done by counting the number of carbon atoms in each of the chains connecting the two atoms that constitute the **ring junctions** or **bridgeheads**. Decalin has *four* carbons in each of two chains and *none* in the third. Therefore, decalin is *bicyclo[4.4.0]decane*. Notice that the numbers are enclosed in square brackets after the prefix "bicyclo" and before the name of the hydrocarbon. The numbers are listed in order of decreasing magnitude and are properly separated by periods, not commas. Some other examples follow:



bicyclo[2.2.1]heptane



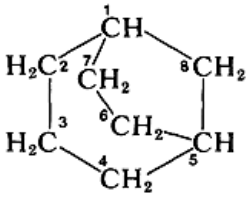
bicyclo[3.1.1]heptane



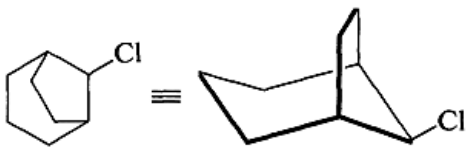
bicyclo[1.1.0]butane

To name substituted polycycloalkanes, a numbering system is required. In the IUPAC system the *main* ring is the one containing the largest number of carbon atoms. Two of the carbons in the main ring serve as junctions for the main bridge, which is chosen to be as large as possible, consistent with the choice of the main ring. Additional rules are required for more complex cases, but these are not of interest to us here.

In numbering bicyclic ring systems that have two ring junctions, one of them is chosen as C1C1. The numbering proceeds along the *longest* chain of carbons to the next junction, then continues along the next longest chain, and finally is completed along the shortest chain. For example,



bicyclo[3.2.1]octane



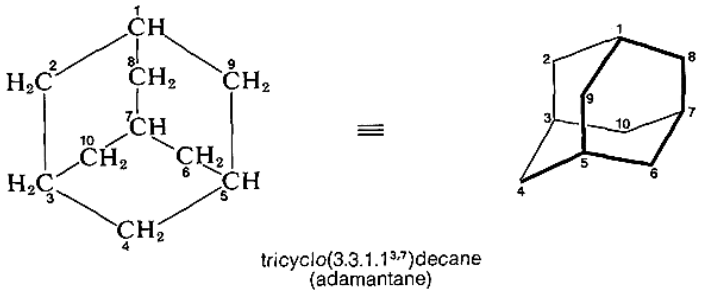
8-chlorobicyclo[3.2.1]octane

Here, the main ring has seven carbons (C1C1 to C7C7) and there is a one-carbon bridge (C8)(C8).

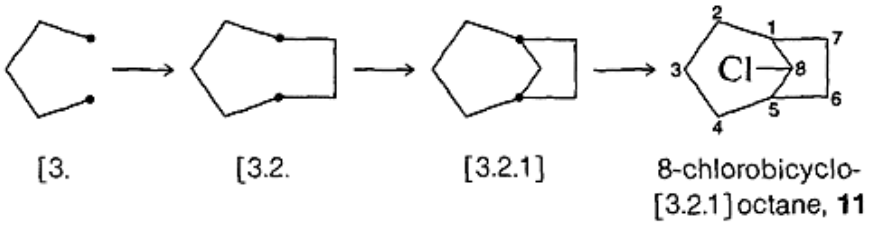
When the hydrocarbon rings have only one carbon in common, they are called *spiranes* and are given systematic names in accord with the following examples:

Notice that for spiranes the numbering starts next to the junction point in the *smaller* ring.

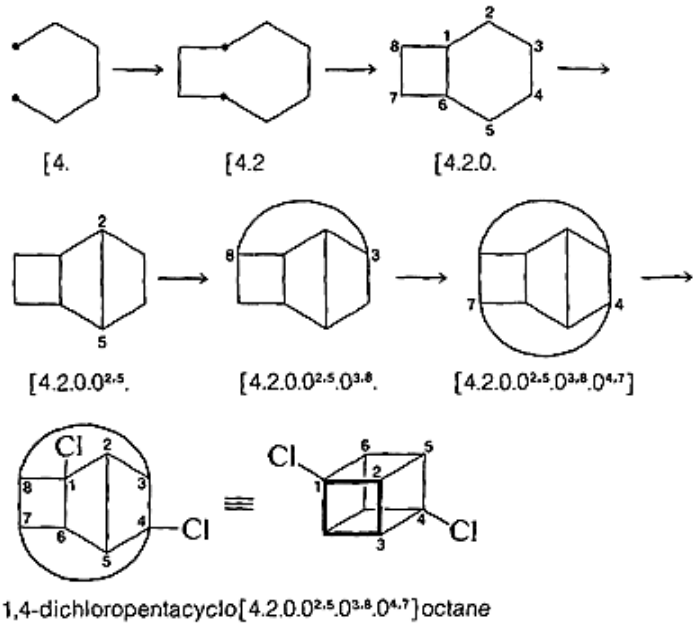
The naming of tricycloalkanes follows the same general system.77 The largest ring and its main linkage form a bicyclic system, and the location of the fourth or *secondary* linkage is shown by superscripts. The systematic name of the interesting hydrocarbon adamantane is given below as an example; its conformation also is shown. The largest ring in adamantane is eight-membered and the carbons that constitute it could be selected in several different ways. The carbon chosen as C9C9 lies between C1C1 and C5C5, not between the higher-numbered C3C3 and C7C7:



To generate a structure from a name such as 8-chlorobicyclo[3.2.1]octane, 1111, start with a pair of junction atoms, connect them as prescribed, then number the initial skeleton, make the final connections, and locate the substituents. The steps follow:



A further and more complicated example is 1,4-dichloropentacyclo[4.2.0.02.52.5.03.83.8.04.74.7]octane:



1,4-dichloropentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane

The most difficult part of the whole procedure may be generating the final structure in appropriate perspective. The task of doing this can be simplified greatly by the use of molecular models.

To determine whether a given bridged polycylic ring system should be *bicyclo-*, *tricyclo-*, and so on, use the rule that the number of rings is equal to the minimum number of bond cleavages to convert the ring system into an *acyclic* hydrocarbon having the same number of carbons.

Free Radical

A **free-radical reaction** is any chemical reaction involving free radicals. This reaction type is abundant in organic reactions. Two pioneering studies into free radical reactions have been the discovery of the triphenylmethyl radical by Moses Gomberg (1900) and the **lead-mirror experiment** described by Friedrich Paneth in 1927. In this last experiment tetramethyllead is decomposed at elevated temperatures to methyl radicals and elemental lead in a quartz tube. The gaseous methyl radicals are moved to another part of the chamber in a carrier gas where they react with lead in a mirror film which slowly disappears.

When radical reactions are part of organic synthesis the radicals are often generated from radical initiators such as peroxides or azobis compounds. Many radical reactions are chain reactions with a chain initiation step, a chain propagation step and a chain termination step. Reaction inhibitors slow down a radical reaction and radical disproportionation is a competing reaction. Radical reactions occur frequently in the gas phase, are often initiated by light, are rarely acid or base catalyzed and are not dependent

on polarity of the reaction medium.[2] Reactions are also similar whether in the gas phase or solution phase

The most important reaction types involving free radicals are:

- Free-radical substitution, for instance free-radical halogenation and autoxidation.
- Free-radical addition reactions
- Intramolecular free radical reactions (substitution or addition) such as the Hofmann–Löffler reaction or the Barton reaction
- Free radical rearrangement reactions are rare compared to rearrangements involving carbocations and restricted to aryl migrations.
- Fragmentation reactions or homolysis, for instance the Norrish reaction, the Hunsdiecker reaction and certain decarboxylations. For fragmentations taking place in mass spectrometry see mass spectrum analysis.
- Electron transfer. An example is the decomposition of certain peresters by Cu(I) which is a one-electron reduction reaction forming Cu(II), an alkoxy oxygen radical and a carboxylate. Another example is Kolbe electrolysis.
- Radical-nucleophilic aromatic substitution is a special case of nucleophilic aromatic substitution.
- Carbon–carbon coupling reactions, for example manganese-mediated coupling reactions.
- Elimination reactions

Free radicals can be formed by photochemical reaction and thermal fission reaction or by oxidation reduction reaction Specific reactions involving free radicals are combustion, pyrolysis and cracking Free radical reactions also occur within and outside of cells, are injurious, and have been implicated in a wide range of human diseases (see 13-Hydroxyoctadecadienoic acid, 9-hydroxyoctadecadienoic acid, reactive oxygen species, and Oxidative stress) as well as many of the maladies associated with ageing

Carbene

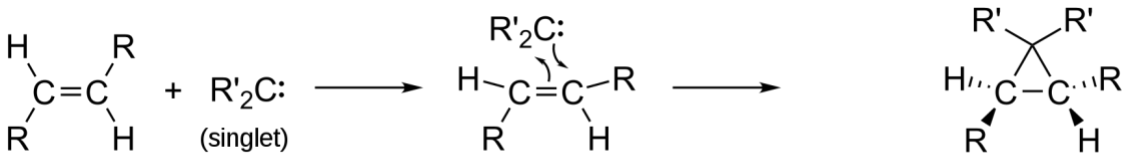
a **carbene** is a molecule containing a neutral carbon atom with a valence of two and two unshared valence electrons. The general formula is R-(C**:**)-R' or R=C**:** where the R represent substituents or hydrogen atoms.

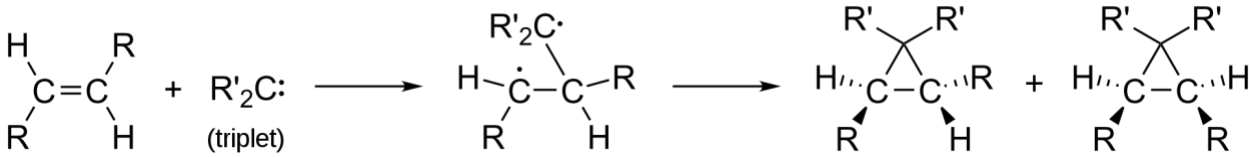
The term "carbene" may also refer to the specific compound H_2C**:**, also called methylene, the parent hydride from which all other carbene compounds are formally derived. Carbenes are classified as either singlets or triplets, depending upon their electronic structure. Most carbenes are very short lived, although persistent carbenes are known. One well-studied carbene is dichlorocarbene Cl_2C**:**, which can be generated *in situ* from chloroform and a strong base.

Singlet and triplet carbenes exhibit divergent reactivity. Singlet carbenes generally participate in cheletropic reactions as either electrophiles or nucleophiles. Singlet carbenes with unfilled p-orbital should be electrophilic. Triplet carbenes can be considered to

be diradicals, and participate in stepwise radical additions. Triplet carbenes have to go through an intermediate with two unpaired electrons whereas singlet carbene can react in a single concerted step.

Due to these two modes of reactivity, reactions of singlet methylene are stereospecific whereas those of triplet methylene are stereoselective. This difference can be used to probe the nature of a carbene. For example, the reaction of methylene generated from photolysis of diazomethane with *cis*-2-butene or with *trans*-2-butene each give a single diastereomer of the 1,2-dimethylcyclopropane product *cis* from *cis* and *trans* from *trans*, which proves that the methylene is a singlet. If the methylene were a triplet, one would not expect the product to depend upon the starting alkene geometry, but rather a nearly identical mixture in each case.

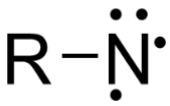




Reactivity of a particular carbene depends on the substituent groups. Their reactivity can be affected by metals. Some of the reactions carbenes can do are insertions into C-H bonds, skeletal rearrangements, and additions to double bonds. Carbenes can be classified as nucleophilic, electrophilic, or ambiphilic. For example, if a substituent is able to donate a pair of electrons, most likely carbene will not be electrophilic. Alkyl carbenes insert much more selectively than methylene, which does not differentiate between primary, secondary, and tertiary C-H bonds.

Nitrene

A nitrene or imene (R–N) is the nitrogen analogue of a carbene. The nitrogen atom is uncharged and univalent, so it has only 6 electrons in its valence level—two covalent bonded and four non-bonded electrons. It is therefore considered an electrophile due to the unsatisfied octet. A nitrene is a reactive intermediate and is involved in many chemical reactions. The simplest nitrene, HN, is called imidogen, and that term is sometimes used as a synonym for the nitrene class.



the linear N–H molecule (imidogen) has its nitrogen atom sp hybridized, with two of its four non-bonded electrons as a lone pair in an sp orbital and the other two occupying a degenerate pair of p orbitals. The electron configuration is consistent with Hund's rule: the low energy form is a triplet with one electron in each of the p orbitals and the high energy form is the singlet with an electron pair filling one p orbital and the other p orbital vacant.

As with carbenes, a strong correlation exists between the spin density on the nitrogen atom which can be calculated in silico and the zero-field splitting parameter *D* which can be derived experimentally from electron spin resonance.Small nitrenes such as NH or CF_3N have D values around 1.8 cm^{-1} with spin densities close to a maximum value of 2. At the lower end of the scale are molecules with low *D* (< 0.4) values and spin density of 1.2 to 1.4 such as 9-anthrylnitrene and 9-phenanthrylnitrene.

Because nitrenes are so reactive, they are not isolated. Instead, they are formed as reactive intermediates during a reaction. There are two common ways to generate nitrenes:

- From azides by thermolysis or photolysis, with expulsion of nitrogen gas. This method is analogous to the formation of carbenes from diazo compounds.
- From isocyanates, with expulsion of carbon monoxide. This method is analogous to the formation of carbenes from ketenes.

carbanion

A **carbanion** is an anion in which carbon is trivalent (forms three bonds) and bears a formal negative charge (in at least one significant resonance form).

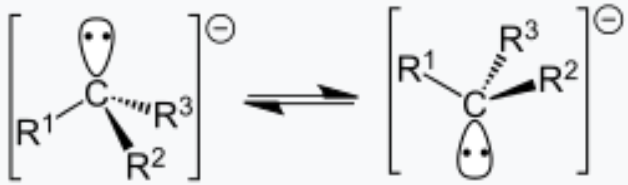
Formally, a carbanion is the conjugate base of a **carbon acid**:

$R_3CH + :B^- \rightarrow \mathbf{R_3C:^-} + HB$

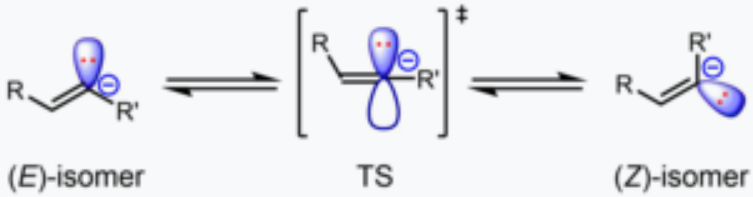
where B stands for the base. The carbanions formed from deprotonation of alkanes (at an sp^3 carbon), alkenes (at an sp^2 carbon), arenes (at an sp^2 carbon), and alkynes (at an sp carbon) are known as **alkyl**, **alkenyl (vinyl)**, **aryl**, and **alkynyl (acetylide) anions**, respectively.

Carbanions have a concentration of electron density at the negatively charged carbon, which, in most cases, reacts efficiently with a variety of electrophiles of varying strengths, including carbonyl groups, imines/iminium salts, halogenating reagents (e.g., *N*-bromosuccinimide and diiodine), and proton donors. A carbanion is one of several reactive intermediates in organic chemistry. In organic synthesis, organolithium reagents and Grignard reagents are commonly treated and referred to as "carbanions." This is a convenient approximation, although these species are generally clusters or complexes containing highly polar, but still covalent bonds metal–carbon bonds ($M^{\delta+}$–$C^{\delta-}$) rather than true carbanions.

Absent π delocalization, the negative charge of a carbanion is localized in an sp^x hybridized orbital on carbon as a lone pair. As a consequence, *localized* alkyl, alkenyl/aryl, and alkynyl carbanions assume trigonal pyramidal, bent, and linear geometries, respectively. By Bent's rule, placement of the carbanionic lone pair electrons in an orbital with significant s character is favorable, accounting for the pyramidalized and bent geometries of alkyl and alkenyl carbanions, respectively. Valence shell electron pair repulsion (VSEPR) theory makes similar predictions. This contrasts with carbocations, which have a preference for unoccupied nonbonding orbitals of pure atomic p character, leading to planar and linear geometries, respectively, for alkyl and alkenyl carbocations.



An alkyl carbanion is trigonal pyramidal.



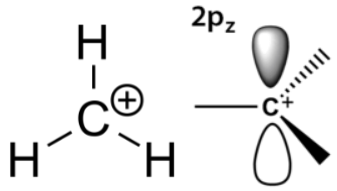
Vinyl anions are bent. 1,2-Disubstituted vinyl anions have *E* and *Z* isomers that undergo inversion through a linear transition state.

However, *delocalized* carbanions may deviate from these geometries. Instead of residing in a hybrid orbital, the carbanionic lone pair may instead occupy a p orbital (or an orbital of high p character). A p orbital has a more suitable shape and orientation to overlap with the neighboring π system, resulting in more effective charge delocalization. As a consequence, alkyl carbanions with neighboring conjugating groups (e.g., allylic anions, enolates, nitronates, etc.) are generally planar rather than pyramidized. Likewise, delocalized alkenyl carbanions sometimes favor a linear instead of bent geometry. More often, a bent geometry is still preferred for substituted alkenyl anions, though the linear geometry is only *slightly* less stable, resulting in facile equilibration between the (*E*) and (*Z*) isomers of the (bent) anion through a linear transition state. For instance, calculations indicate that the parent vinyl anion, $H_2C{=}CH^{\ominus}$, has an inversion barrier of 27 kcal/mol, while allenyl anion, $H_2C{=}C{=}CH^{\ominus}$ ($\leftrightarrow H_2C^{\ominus}{-}C{\equiv}CH$), whose negative charge is stabilized by delocalization, has an inversion barrier of only 4 kcal/mol, reflecting stabilization of the linear transition state by better π delocalization.

carbocation

A **carbocation** is an ion with a positively charged carbon atom. Among the simplest examples are the methenium CH^+_3, methanium CH^+_5 and vinyl $C_2H^+_3$ cations. Occasionally, carbocations that bear more than one positively charged carbon atom are also encountered (e.g., ethylene dication $C_2H^{2+}_4$).

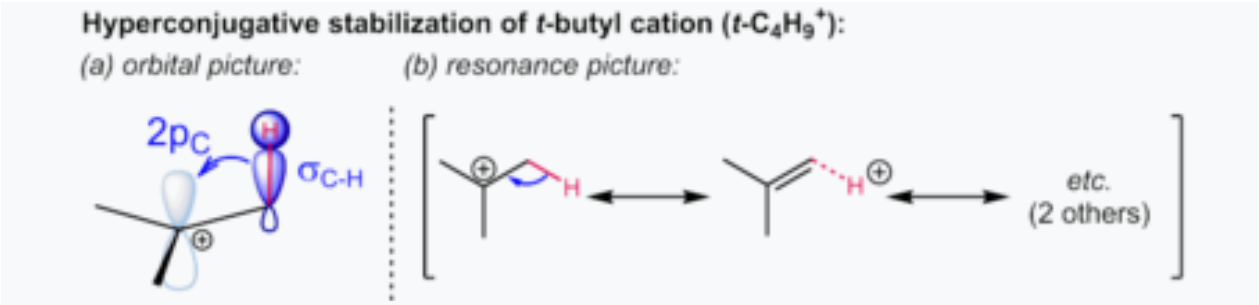
Until the early 1970s, all carbocations were called *carbonium ions*. In the present-day definition given by the IUPAC, a carbocation is any even-electron cation with significant partial positive charge on a carbon atom. They are further classified in two main categories according to the coordination number of the charged carbon: three in the carbenium ions and five in the carbonium ions. Carbonium ions, as originally defined by Olah, are characterized by a three-center two-electron delocalized bonding scheme and are essentially synonymous with so-called 'nonclassical carbocations', which are carbocations that contain bridging C–C or C–H σ-bonds. However, others have more narrowly defined the term 'carbonium ion' as formally protonated or alkylated alkanes (i.e., CR_5^+, where R is hydrogen or alkyl), to the exclusion of nonclassical carbocations like the 2-norbornyl cation



Carbonium ions can be thought of as protonated alkanes. Although alkanes are usually considered inert, under superacid conditions (e.g., HF/SbF_5), the C-H sigma bond can act as a donor to H^+. This results in a species that contains a 3c-2e bond between a carbon and two hydrogen atoms, a type of bonding common in boron chemistry, though relatively uncommon for carbon. As an alternative view point, the 3c-2e bond of carbonium ions could be considered as a molecule of H_2 coordinated to a carbenium ion. Indeed, carbonium ions frequently decompose by loss of molecular hydrogen to form the corresponding carbenium ion. Structurally, the methanium ion CH_5^+ is computed to have a minimum energy structure of C_s symmetry. However, the various possible structures of the ion are close in energy and separated by shallow barriers. Hence, the structure of the ion is often described as fluxional. Although there appear to be five bonds to carbon in carbonium ions, they are not hypervalent, as the electron count around the central carbon is only eight, on account of the 3c-2e bond.

The charged carbon atom in a carbenium ion is a "sextet", i.e. it has only six electrons in its outer valence shell instead of the eight valence electrons that ensures maximum stability (octet rule). Therefore, carbocations are often reactive, seeking to fill the octet of valence electrons as well as regain a neutral charge. In accord with VSEPR and Bent's rule, unless geometrically constrained to be pyramidal (e.g., 1-adamantyl cation), 3-coordinate carbenium ions are usually trigonal planar, with a pure p character empty orbital as its

lowest unoccupied molecular orbital and CH/CC bonds formed from C(sp^2) orbitals. A prototypical example is the methyl cation, CH^+_3. For the same reasons, carbocations that are 2-coordinate (vinyl cations) are generally linear in geometry, with CH/CC bonds formed from C(sp) orbitals.



Hyperconjugation by neighboring alkyl groups stabilizes the *t*-butyl cation. The stabilizing interaction can be depicted as an orbital interaction or by resonance structures involving "no-bond" resonance forms. (For clarity, a dashed line is used to show that the hydrogen atom is still attached, although the formal C–H bond order in the hyperconjugative structure is zero.)

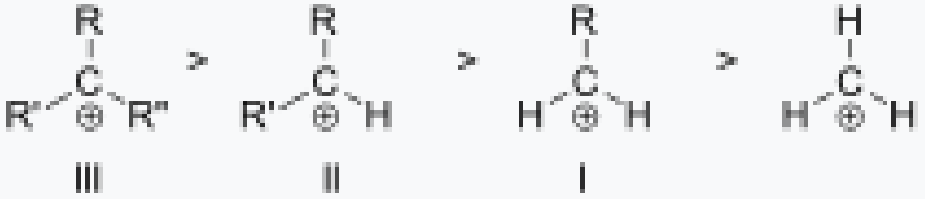
Alkyl-substituted carbocations follow the order 3° > 2° > 1° > methyl in stability, as can be inferred by the hydride ion affinity values (231, 246, 273, and 312 kcal/mol for $(CH_3)_3C^+$, $(CH_3)_2CH^+$, $C_2H_5^+$, and CH_3^+).The effect of alkyl substitution is a strong one: tertiary cations are stable and many are directly observable in superacid media, but secondary cations are usually transient and only the isopropyl, *s*-butyl, and cyclopentyl cations have been observed in solution. There is seldom any experimental support for primary carbocations in the solution phase, even as transient intermediates (the ethyl cation has been proposed for reactions in 99.9% sulfuric acid and in FSO_2OH-SbF_5), and methyl cation has only been unambiguously identified in the gas phase. In most, if not all cases, the ground state of alleged primary carbocations consist of bridged structures in which positive charge is shared by two or more carbon atoms and are better described as side-protonated alkenes, edge-protonated cyclopropanes, or corner-protonated cyclopropanes rather than true primary cations. Even the simple ethyl cation, $C_2H_5^+$, has been demonstrated experimentally and computationally to be bridged and can be thought of as a symmetrically protonated ethylene molecule. The same is true for higher homologues like *n*-propyl cation. Neopentyl derivatives are thought to ionize with concomitant migration of a methyl group (anchimeric assistance); thus, in most if not all cases, a discrete neopentyl cation is not believed to be involved.

The stabilization by alkyl groups is explained by hyperconjugation. The donation of electron density from a β C-H or C-C bond into the unoccupied p orbital of the carbocation (a $\sigma_{CH/CC} \rightarrow$ p interaction) allows the positive charge to be delocalized.

Based on hydride ion affinity, the parent vinyl cation is less stable than even a primary sp^2-hybridized carbocation, while an α alkyl-substituted vinyl cation has a stability that is comparable to the latter. Hence, vinyl cations are relatively uncommon intermediates. They can be generated by the ionization of a vinyl electrophile, provided the leaving group is sufficiently good (e.g., TfO^-, IPh, or N_2). They have been implicated as intermediates in some vinyl substitution reactions (designated as S_N1(vinyl)) and as intermediates in the electrophilic addition reactions of arylalkynes. With the exception of the parent vinyl cation, which is believed to be a bridged species, and geometrically constrained cyclic vinyl cations, most vinyl cations take on sp-hybridization and are linear.

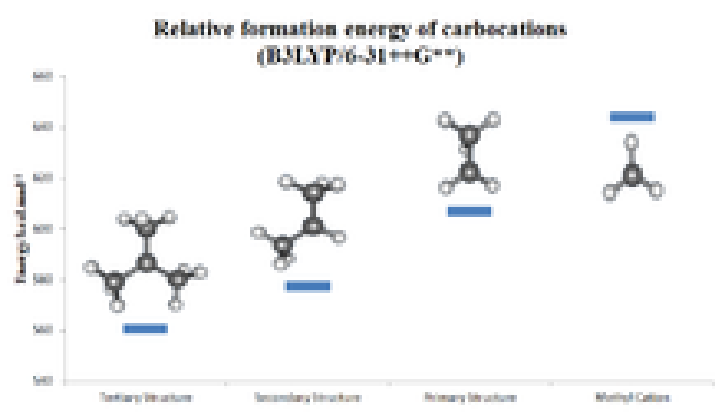
Aryl cations are more unstable than vinyl cations, due to the ring-enforced distortion to a nonlinear geometry and approximately sp^2-character of the unoccupied orbital. Only N_2 in aryldiazonium salts is a good enough leaving group for the chemical generation of aryl cations.

Alkynyl cations are extremely unstable, much less stable than even CH_3^+ (hydride ion affinity 386 kcal/mol vs. 312 kcal/mol for CH_3^+) and cannot be generated by purely chemical means. They can, however, be generated radio chemically via the beta decay of tritium: ($RC{\equiv}CT \rightarrow [RC{\equiv}C^3He]^+ + e^- + \nu_e \rightarrow RC{\equiv}C^+ + {}^3He + e^- + \nu_e$).[29]



Order of stability of examples of tertiary (III), secondary (II), and primary (I) alkyl carbenium ions, as well as the methyl cation (far right).

In terms of reactivity, carbocations are susceptible to attack by nucleophiles, like water, alcohols, carboxylates, azide, and halide ions, to form the addition product. Strongly basic nucleophiles, especially hindered ones, favor elimination over addition. Because even weak nucleophiles will react with carbocations, most can only be directly observed or isolated in non-nucleophilic media like superacids.



Relative formation energy of carbocations from computational calculation

Carbocations typically undergo rearrangement reactions from less stable structures to equally stable or more stable ones by migration of an alkyl group or hydrogen to the cationic center to form a new carbocationic center. This often occurs with rate constants in excess of 10^{10} s^{-1} at ambient temperature and still takes place rapidly (compared to the NMR timescale) at temperatures as low as –120 °C (*see Wagner-Meerwein shift*). In especially favorable cases like the 2-norbornyl cation, hydrogen shifts may still take place at rates fast enough to interfere with X-ray crystallography at 86 K (–187 °C). Typically, carbocations will rearrange to give a tertiary isomer. For instance, all isomers of $C_6H_{12}^+$ rapidly rearrange to give the 1-methyl-1-cyclopentyl cation. This fact often complicates synthetic pathways. For example, when 3-pentanol is heated with aqueous HCl, the initially formed 3-pentyl carbocation rearranges to a statistical mixture of the 3-pentyl and 2-pentyl. These cations react with chloride ion to produce about ⅓ 3-chloropentane and ⅔ 2-chloropentane. The Friedel-Crafts alkylation suffers from this limitation; for this reason, the acylation (followed by Wolff-Kishner or Clemmensen reduction to give the alkylated product) is more frequently applied.

A carbocation may be stabilized by resonance by a carbon-carbon double bond next to the ionized carbon. Such cations as *allyl* cation $CH_2{=}CH{-}CH_2^+$ and *benzyl* cation $C_6H_5{-}CH_2^+$ are more stable than most other carbocations due to donation of electron density from π systems to the cationic center. Molecules that can form allyl or benzyl carbocations are especially reactive. These carbocations where the C^+ is adjacent to another carbon atom that has a double or triple bond have extra stability because of the overlap of the empty p orbital of the carbocation with the p orbitals of the π bond. This overlap of the orbitals allows the positive charge to be dispersed and electron density from the π system to be shared with the electron-deficient center, resulting in stabilization. The doubly- and triply-benzylic carbocations, diphenylcarbenium and triphenylcarbenium (trityl) cation, are particularly stable. For the same reasons, the partial p character of strained C–C bonds in cyclopropyl groups also allows for donation of electron density and stabilizes the *cyclopropylmethyl* (cyclopropylcarbinyl) cation.

As noted in the history section, the tropylium cation ($C_7H_7^+$) was one of the first carbocations to be discovered, due to its aromatic stability. On the other hand, the anti-

aromatic cyclopentadienylium cation ($C_5H_5^+$) is destabilized by some 50 kcal/mol. The cyclopropenium cation ($C_3H_3^+$), although somewhat destabilized by angle strain, is still clearly stabilized by aromaticity when compared to its open-chain analog, allyl cation.

Nitrenium ion

A **Nitrenium ion** (also called: **aminylium ion**) in organic chemistry is a reactive intermediate based on nitrogen with both an electron lone pair and a positive charge and with two substituents (R_2N^+). Nitrenium ions are isoelectronic with carbenes, and can exist in either a singlet or a triplet state. The parent nitrenium ion, NH^+_2, is a ground state triplet species with a gap of 30 kcal/mol (130 kJ/mol) to the lowest energy singlet state. Conversely, most arylnitrenium ions are ground state singlets. Certain substituted arylnitrenium ions can be ground state triplets, however.

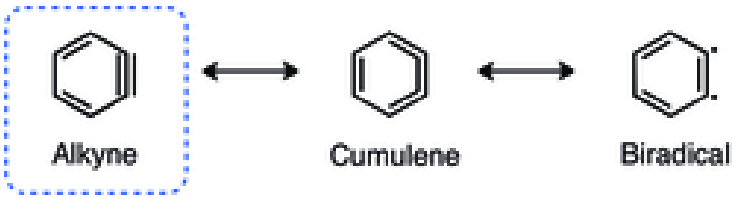
Aryl nitrenium ions are currently investigated because of their involvement in certain DNA damaging processes. These intermediates can have microsecond or longer lifetimes in water. They can also be exploited for useful synthetic processes.

Nitrenium ions are also intermediates in organic reactions; for instance, the Bamberger rearrangement. They can also act as electrophiles in electrophilic aromatic substitution

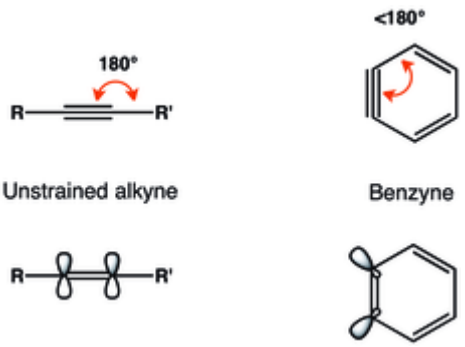
Arynes

Arynes or **benzynes** are highly reactive species derived from an aromatic ring by removal of two substituents. The most common arynes are ortho but meta- and para-arynes are also known. *o*-Arynes are examples of strained alkynes.

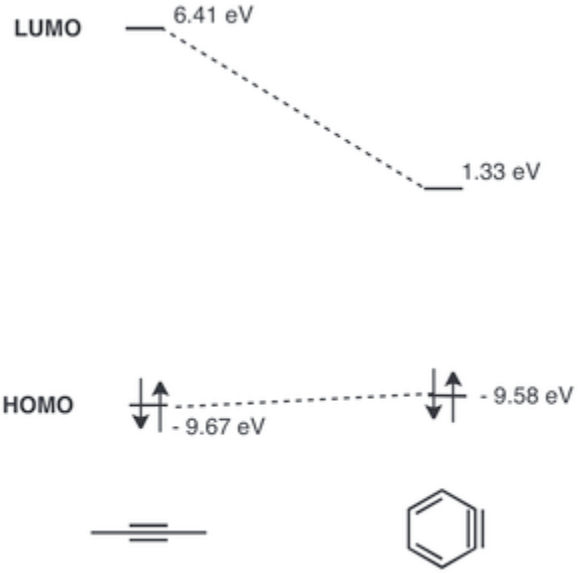
The alkyne representation of benzyne is the most widely encountered. o-Arynes, or 1,2-didehydroarenes, are usually described as having a strained triple bond.



Geometric constraints on the triple bond in *ortho*-benzyne result in diminished overlap of in-plane p-orbitals, and thus weaker triple bond. The vibrational frequency of the triple bond in benzyne was assigned by Radziszewski to be 1846 cm^{-1}, indicating a weaker triple bond than in unstrained alkyne with vibrational frequency of approximately 2150 cm^{-1}. Nevertheless, *ortho*-benzyne is more like a strained alkyne than a biradical, as seen from the large singlet–triplet gap and alkyne-like reactivity.

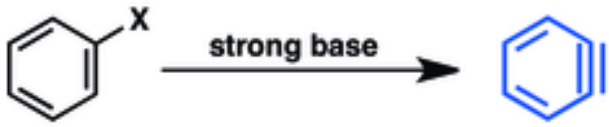


The LUMO of aryne lies much lower than the LUMO of unstrained alkynes, which makes it a better energy match for the HOMO of nucleophiles. Hence, benzyne possesses electrophilic character and undergoes reactions with nucleophiles. A detailed MO analysis of benzyne was presented in 1968.

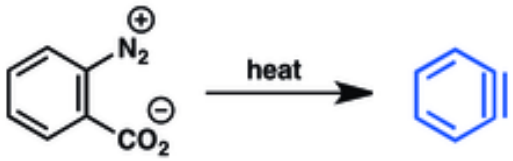


Due to their extreme reactivity, arynes must be generated *in situ*. Typical of other reactive intermediates, benzyne must be trapped, otherwise it dimerises to biphenylene.

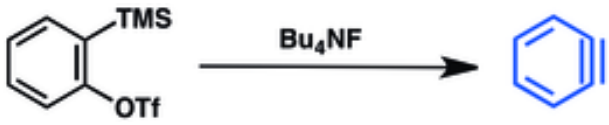
Early routes to benzyne involved dehydrohalogenation of aryl halides:



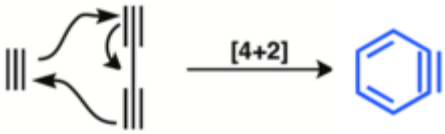
Such reactions require strong base and high temperatures. Ortho-disubstituted arenes serve as precursors to benzynes under milder conditions. Benzyne is generated by the dehalogenation of 2-bromofluorobenzene by magnesium. Anthranilic acid can be converted to 2-diazoniobenzene-1-carboxylate by diazotization and neutralization. Although explosive, this zwitterionic species is a convenient and inexpensive precursor to benzyne.



Another method is based on trimethylsilylaryl triflates.Fluoride displacement of the trimethylsilyl group induces elimination of triflate and release of benzyne:



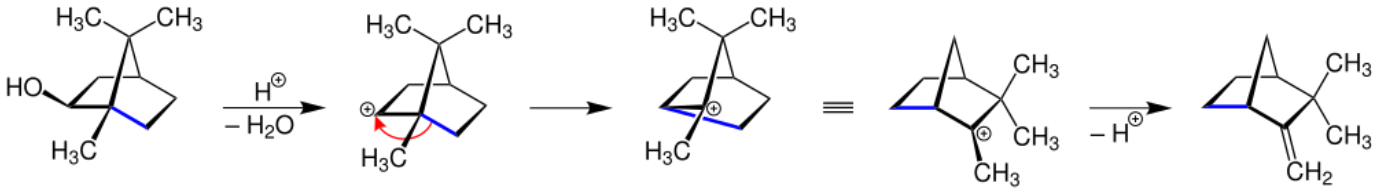
A hexadehydro Diels-Alder reaction (HDDA) involves cycloaddition of 1,3-diyne and alkyne.



Wagner-meerwein rearrangement

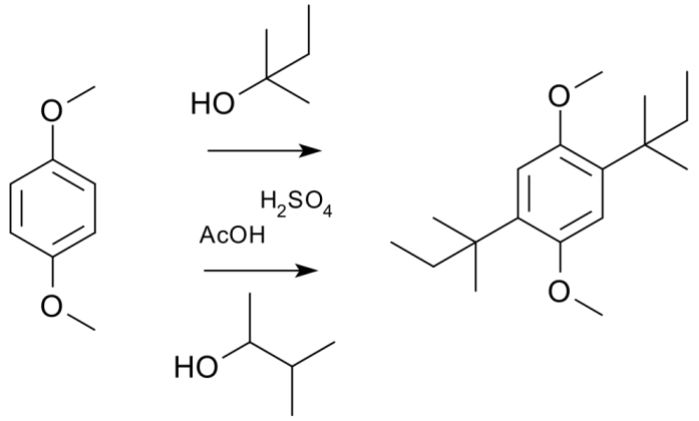
A **Wagner–Meerwein rearrangement** is a class of carbocation 1,2-rearrangement reactions in which a hydrogen, alkyl or aryl group migrates from one carbon to a neighboring carbon. They can be described as cationic [1,2]-sigmatropic rearrangements, proceeding suprafacially and with stereochemical retention. As such, a Wagner–Meerwein shift is a thermally allowed pericyclic process with the Woodward-Hoffmann symbol . They are usually facile, and in many cases, they can take place at temperatures as low as –120 °C. The reaction is named after the Russian chemist Yegor Yegorovich Vagner; he had German origin and published in German journals as Georg Wagner; and Hans Meerwein.

The rearrangement was first discovered in bicyclic terpenes for example the conversion of isoborneol to camphene.



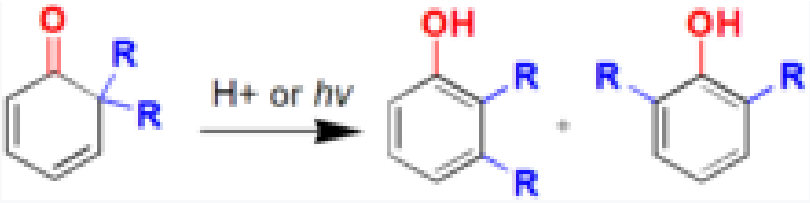
The story of the rearrangement reveals that many scientists were puzzled with this and related reactions and its close relationship to the discovery of carbocations as intermediates.

In a simple demonstration reaction of 1,4-dimethoxybenzene with either 2-methyl-2-butanol or 3-methyl-2-butanol in sulfuric acid and acetic acid yields the same disubstituted product, the latter via a hydride shift of the cationic intermediate:



Dienone-phenol rearrangement

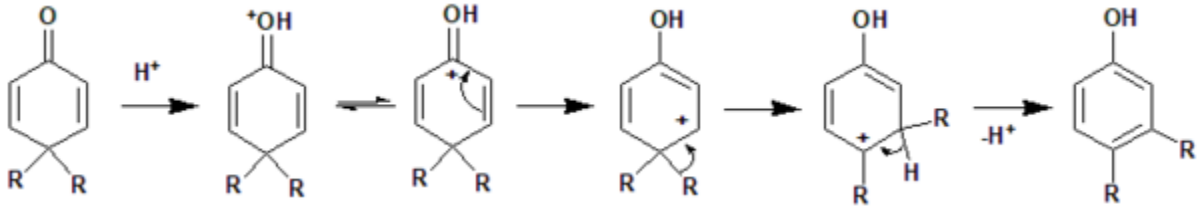
The **dienone-phenol rearrangement** is a reaction in organic chemistry first reported in 1921 by Auwers and Ziegler. A common example of dienone-phenol rearrangement is 4,4-disubstituted cyclohexadienone converting into a stable 3,4-disubstituted phenol in presence of acid. A similar rearrangement is possible with 2,2-disubstituted cyclohexadienone to its corresponding disubstituted phenol. Usually this type rearrangement is a spontaneous unless the presence of a dichloromethyl group at 3rd position or 4th position is blocked with any non hydrogen groups.



Dienone-phenol rearrangement of 2,2-disubstituted cyclohexadienone

Mechanism

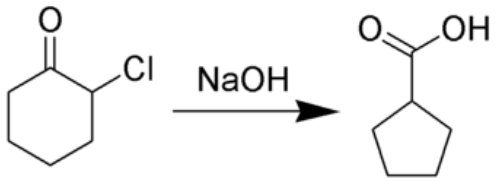
The reaction mechanism of 4,4-disubstituted cyclohexadienones to 3,4-disubstituted phenol is illustrated here.



The migration tendency for the two different groups (R) present at either 4,4 position or 2,2 position can be determined by comparing the relative stability of intermediate Carbocation formed in the time of rearrangement. In case of acid-promoted conditions, the migration tendencies few groups are like this COOEt > Phenyl (or alkyl); Phenyl > Methyl; vinyl > Methyl; Methyl > alkoxy and alkoxy > Phenyl. In some cases such as allyl and benzyl group, the actual rearrangement might undergo through the Cope Rearrangement. Apart from acid catalysis, the dienone-phenol rearrangement is also possible in presence of base. The dienone-phenol rearrangement found helpful in various synthetic protocols use towards the synthesis of steroids, anthracene, phenanthrene, etc.

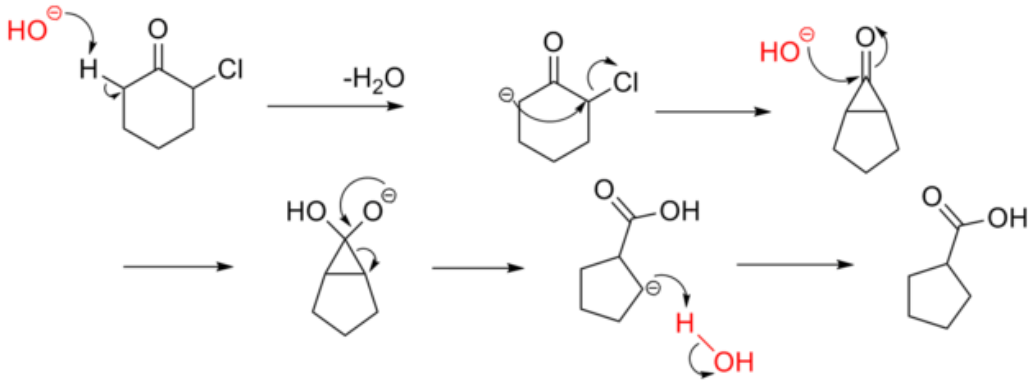
Favorskii rearrangement

The **Favorskii rearrangement**, named for the Russian chemist Alexei Yevgrafovich Favorskii, is most principally a rearrangement of cyclopropanones and α-halo ketones which leads to carboxylic acid derivatives. In the case of cyclic α-halo ketones, the Favorskii rearrangement constitutes a ring contraction. This rearrangement takes place in the presence of a base, sometimes hydroxide, to yield a carboxylic acid but most of the time either an alkoxide base or an amine to yield an ester or an amide, respectively. α,α'-Dihaloketones eliminate HX under the reaction conditions to give α,β-unsaturated carbonyl compounds.



Mechanism

The reaction mechanism is thought to involve the formation of an enolate on the side of the ketone away from the chlorine atom. This enolate cyclizes to a cyclopropanone intermediate which is then attacked by the hydroxide nucleophile.



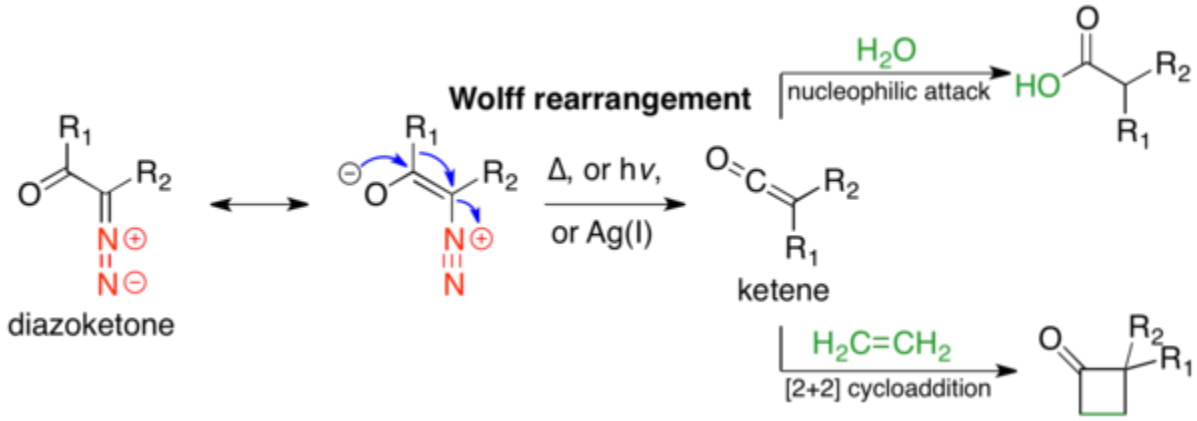
The second step has also been proposed to be stepwise process, with chloride anion leaving first to produce a zwitterionic oxyallyl cation before a disrotatory electrocyclic ring closure takes place to afford the cyclopropanone intermediate.

Usage of alkoxide anions such as sodium methoxide, instead of sodium hydroxide, yields the ring-contracted ester product.

When enolate formation is impossible, the Favorskii rearrangement takes place by an alternate mechanism, in which addition to hydroxide to the ketone takes place, followed by concerted collapse of the tetrahedral intermediate and migration of the neighboring carbon with displacement of the halide. This is sometimes known as the pseudo-Favorskii rearrangement, although previous to labeling studies, it was thought that all Favorskii rearrangements proceeded through this mechanism

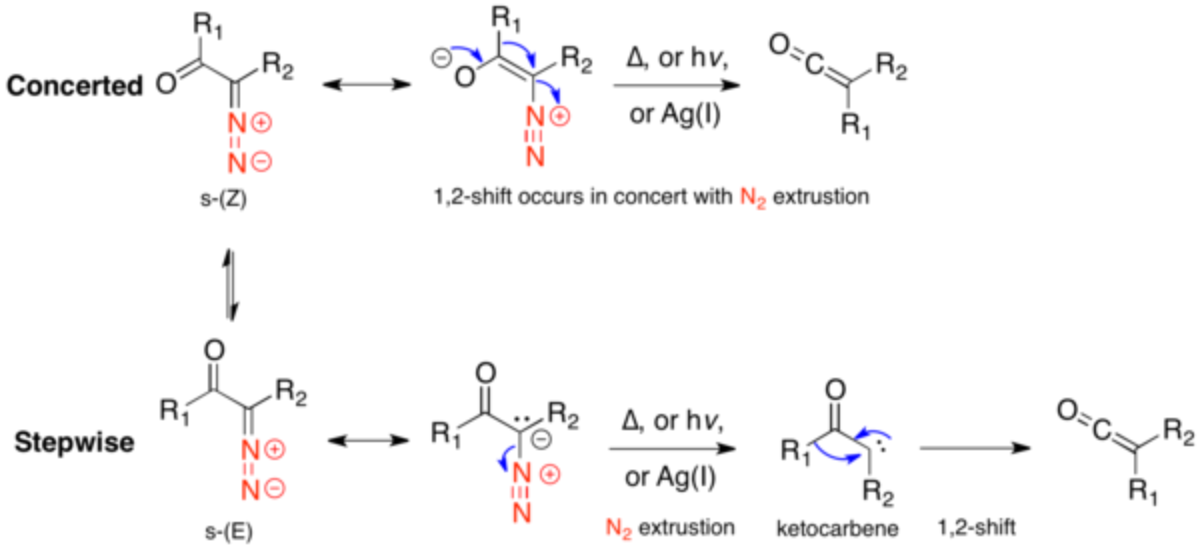
Wolff rearrangement

The **Wolff rearrangement** is a reaction in organic chemistry in which an α-diazocarbonyl compound is converted into a ketene by loss of dinitrogen with accompanying 1,2-rearrangement. The Wolff rearrangement yields a ketene as an intermediate product, which can undergo nucleophilic attack with weakly acidic nucleophiles such as water, alcohols, and amines, to generate carboxylic acid derivatives or undergo [2+2] cycloaddition reactions to form four-membered rings. The mechanism of the Wolff rearrangement has been the subject of debate since its first use. No single mechanism sufficiently describes the reaction, and there are often competing concerted and carbene-mediated pathways; for simplicity, only the textbook, concerted mechanism is shown below. The reaction was discovered by Ludwig Wolff in 1902. The Wolff rearrangement has great synthetic utility due to the accessibility of α-diazocarbonyl compounds, variety of reactions from the ketene intermediate, and stereochemical retention of the migrating group. However, the Wolff rearrangement has limitations due to the highly reactive nature of α-diazocarbonyl compounds, which can undergo a variety of competing reactions.



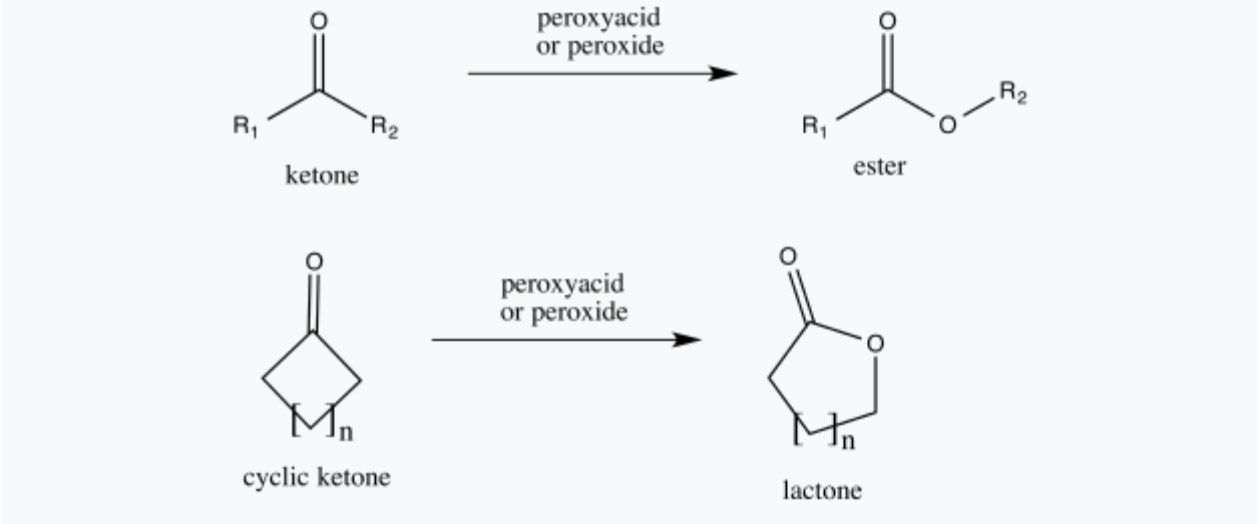
Mechanism

The mechanistic pathway of the Wolff-rearrangement has been the subject of much debate, as there are often competing concerted and stepwise mechanisms. However, two aspects of the mechanism can be agreed upon. First, α-diazocarbonyl compounds are in an equilibrium of s-*cis* and s-*trans*-conformers, the distribution of which may influence the mechanism of the reaction. Generally, under photolysis, compounds in the s-*cis* conformation react in a concerted manner due to the antiperiplanar relationship between the leaving and migrating groups, whereas compounds in the s-*trans* conformation react stepwise through a carbene intermediate or do not rearrange. Second, regardless of the reaction mechanism, the rearrangement gives a ketene intermediate, which can be trapped by a weakly acidic nucleophile, such as an alcohol or amine, to give the corresponding ester or amide, or an olefin, to give a [2+2] cycloaddition adduct. Strong acids do not rearrange, but rather protonate the α-carbon and give S_N2 products.



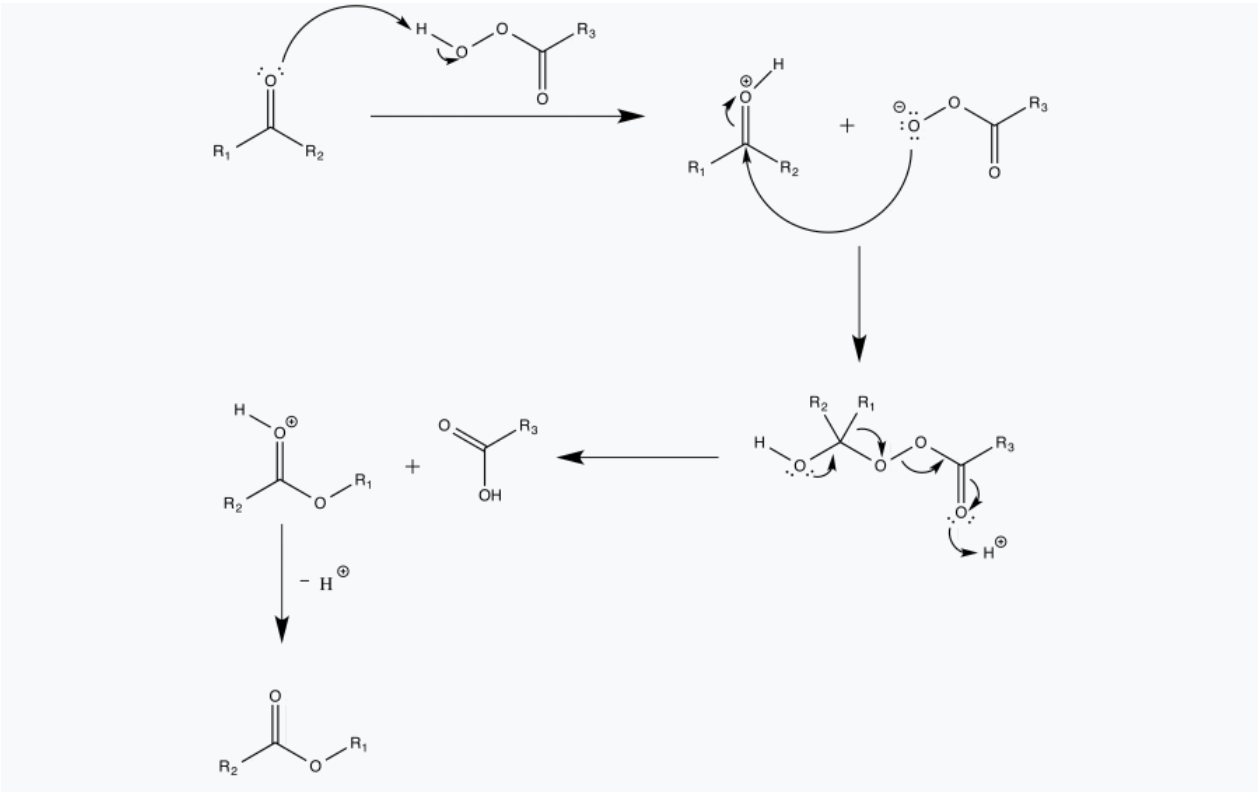
Baeyer–Villiger rearrangement

The **Baeyer–Villiger oxidation** is an organic reaction that forms an ester from a ketone or a lactone from a cyclic ketone, using peroxyacids or peroxides as the oxidant. The reaction is named after Adolf von Baeyer and Victor Villiger who first reported the reaction in 1899.



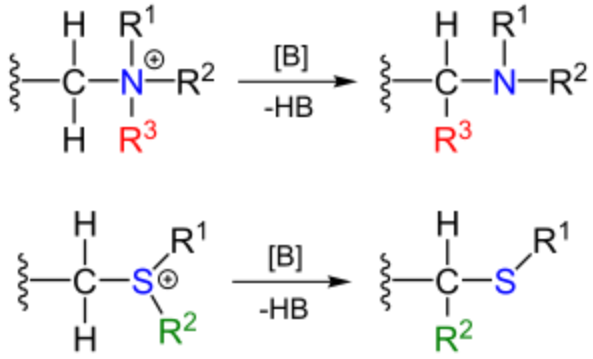
Mechanism

In the first step of the reaction mechanism, the peroxyacid protonates the oxygen of the carbonyl group. This makes the carbonyl group more susceptible to be attacked by the peroxyacid. Next, the peroxyacid attacks the carbon of the carbonyl group forming what is known as the Criegee intermediate. Through a concerted mechanism, one of the substituents on the ketone migrates to the oxygen of the peroxide group while a carboxylic acid leaves. This migration step is thought to be the rate determining step. Finally, deprotonation of the oxocarbenium ion produces the ester.



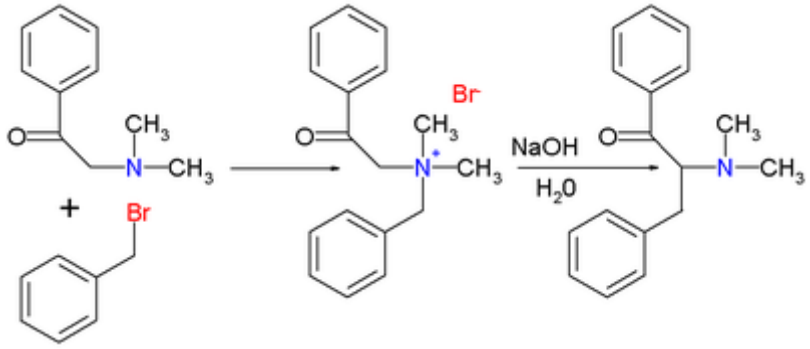
Stevens rearrangement

The **Stevens rearrangement** in organic chemistry is an organic reaction converting quaternary ammonium salts and sulfonium salts to the corresponding amines or sulfides in presence of a strong base in a 1,2-rearrangement.



The reactants can be obtained by alkylation of the corresponding amines and sulfides. The substituent **R** next the amine methylene bridge is an electron-withdrawing group.

The original 1928 publication by Thomas S. Stevens concerned the reaction of *1-phenyl-2-(N,N-dimethylamino)ethanone* with benzyl bromide to the ammonium salt followed by the rearrangement reaction with sodium hydroxide in water to the rearranged amine.

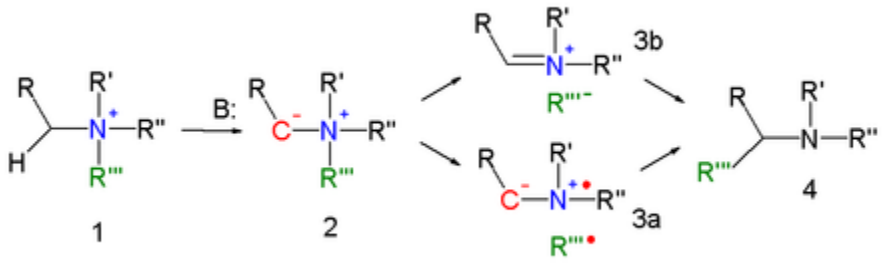


Mechanism

The reaction mechanism of the Stevens rearrangement is one of the most controversial reaction mechanisms in organic chemistry. Key in the reaction mechanism for the Stevens rearrangement (explained for the nitrogen reaction) is the formation of an ylide after deprotonation of the ammonium salt by a strong base. Deprotonation is aided by electron-withdrawing properties of substituent R. Several reaction modes exist for the actual rearrangement reaction.

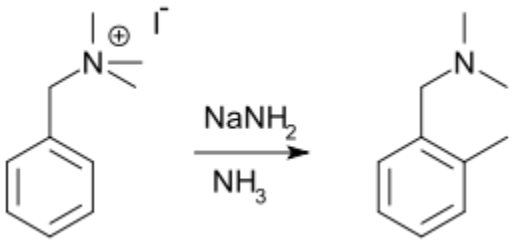
A concerted reaction requires an antarafacial reaction mode but since the migrating group displays retention of configuration this mechanism is unlikely.

In an alternative reaction mechanism the N–C bond of the leaving group is homolytically cleaved to form a di-radical pair (**3a**). In order to explain the observed retention of configuration, the presence of a solvent cage is invoked. Another possibility is the formation of a cation-anion pair (**3b**), also in a solvent cage.



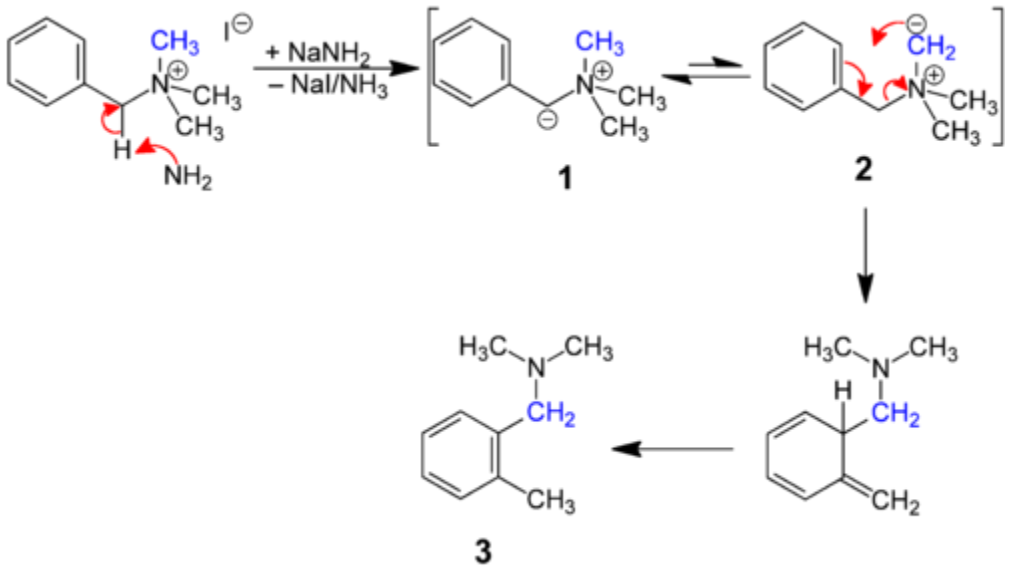
Sommelet–Hauser rearrangement

The **Sommelet–Hauser rearrangement** (named after M. Sommelet and Charles R. Hauser) is a rearrangement reaction of certain benzyl quaternary ammonium salts. The reagent is sodium amide or another alkali metal amide and the reaction product a *N*,*N*-dialkylbenzylamine with a new alkyl group in the aromatic ortho position. For example, benzyltrimethylammonium iodide, $[(C_6H_5CH_2)N(CH_3)_3]I$, rearranges in the presence of sodium amide to yield the *o*-methyl derivative of *N*,*N*-dimethylbenzylamine.



Mechanism

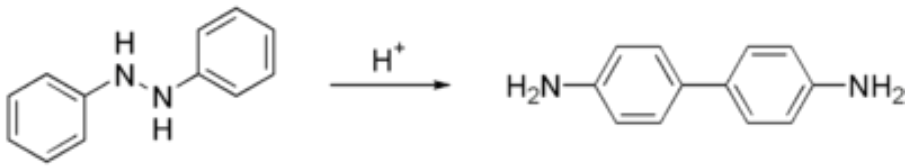
The benzylic methylene proton is acidic and deprotonation takes place to produce the benzylic ylide (**1**). This ylide is in equilibrium with a second ylide that is formed by deprotonation of one of the ammonium methyl groups (**2**). Though the second ylide is present in much smaller amounts, it undergoes a 2,3-sigmatropic rearrangement and subsequent aromatization to form the final product (**3**).



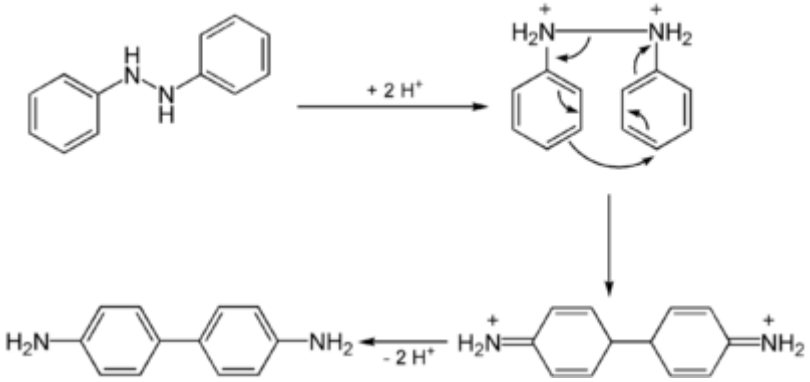
The Stevens rearrangement is a competing reaction.

Benzidine rearrangement

Benzidine is prepared in a two step process from nitrobenzene. First, the nitrobenzene is converted to 1,2-diphenylhydrazine, usually using iron powder as the reducing agent. Treatment of this hydrazine with mineral acids induces a rearrangement reaction to 4,4'-benzidine. Smaller amounts of other isomers are also formed. The **benzidine rearrangement**, which proceeds intramolecularly, is a classic mechanistic puzzle in organic chemistry.



The conversion is described as a [5,5]sigmatropic reaction.



In terms of its physical properties, 4,4'-benzidine is poorly soluble in cold water but can be recrystallized from hot water, where it crystallises as the monohydrate. It is dibasic, the deprotonated species has K_a values of 9.3×10^{-10} and 5.6×10^{-11}. Its solutions react with oxidizing agents to give deeply coloured quinone-related derivatives.

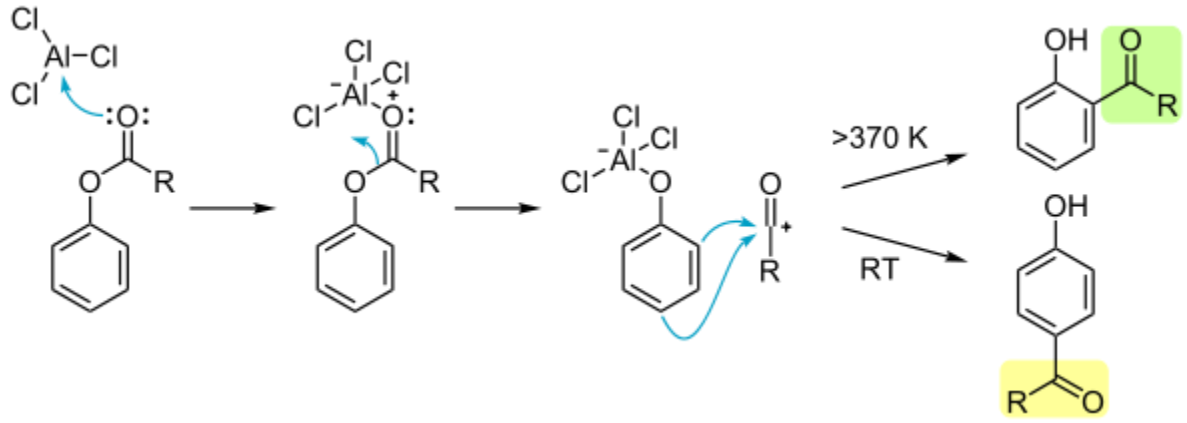
Fries rearrangement

The **Fries rearrangement**, named for the German chemist Karl Theophil Fries, is a rearrangement reaction of a phenolic ester to a hydroxy aryl ketone by catalysis of Lewis acids.

It involves migration of an acyl group of phenol ester to the aryl ring. The reaction is ortho and para selective and one of the two products can be favoured by changing reaction conditions, such as temperature and solvent.

Mechanism

Despite many efforts, a definitive reaction mechanism for the Fries rearrangement has not been determined. Evidence for inter- and intramolecular mechanisms have been obtained by crossover experiments with mixed reactants. The Reaction progress is not dependent on solvent or substrate. A widely accepted mechanism involves a carbocation intermediate.

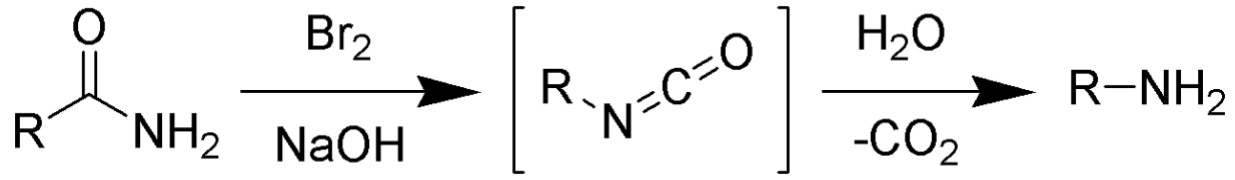


In the first reaction step a Lewis acid for instance aluminium chloride $AlCl_3$ co-ordinates to the carbonyl oxygen atom of the acyl group. This oxygen atom is more electron rich than the phenolic oxygen atom and is the preferred Lewis base. This interaction polarizes the bond between the acyl residue and the phenolic oxygen atom and the aluminium chloride group rearranges to the phenolic oxygen atom. This generates a free acylium carbocation which reacts in a classical electrophilic aromatic substitution with the aromatic ring. The abstracted proton is released as hydrochloric acid where the chlorine is derived from aluminium chloride. The orientation of the substitution reaction is temperature dependent. A low reaction temperature favors para substitution and with high temperatures the ortho product prevails, this can be rationalised as exhibiting classic Thermodynamic versus kinetic reaction control as the ortho product can form a more stable bidentate complex with the Aluminium. Formation of the ortho

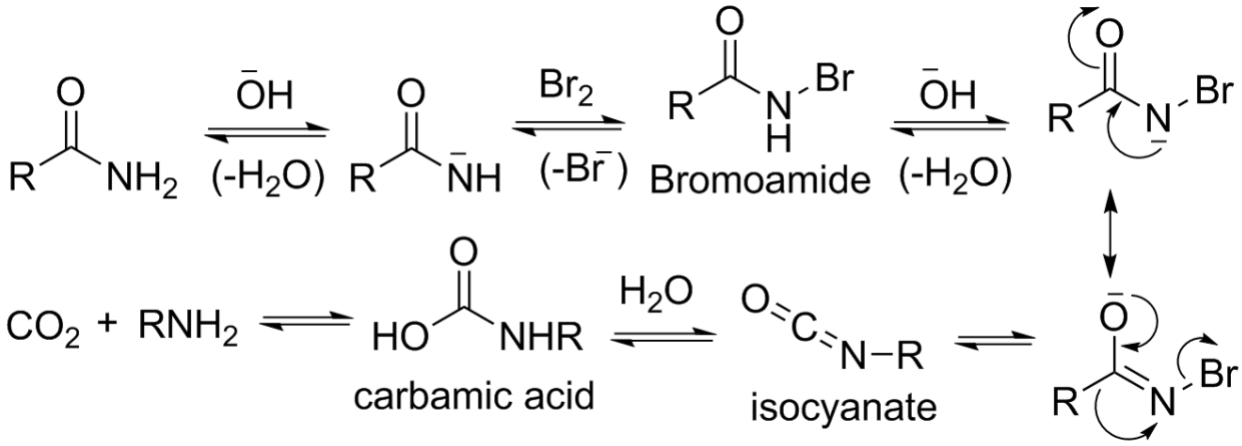
product is also favoured in non-polar solvents; as the solvent polarity increases, the ratio of the para product also increases.

Hofmann rearrangement

The reaction of bromine with sodium hydroxide forms sodium hypobromite *in situ*, which transforms the primary amide into an intermediate isocyanate. The formation of an intermediate nitrene is not possible because it implies also the formation of a hydroxamic acid as a byproduct, which has never been observed. The intermediate isocyanate is hydrolyzed to a primary amine, giving off carbon dioxide.



Mechanism



1. Base abstracts an acidic N-H proton, yielding an anion.
2. The anion reacts with bromine in an α-substitution reaction to give an *N*-bromoamide.
3. Base abstraction of the remaining amide proton gives a bromoamide anion.
4. The bromoamide anion rearranges as the R group attached to the carbonyl carbon migrates to nitrogen at the same time the bromide ion leaves, giving an isocyanate.
5. The isocyanate adds water in a nucleophilic addition step to yield a carbamic acid (aka urethane).
6. The carbamic acid spontaneously loses CO_2, yielding the amine product.

Examples

UNIT – II

Thermodynamic and Kinectic Aspects of Organic Reactions

2 Marks

1. Sketch energy profile diagram.
2. Difference between intermediate and transition state
3. What is isotopic effect?
4. What is ment by grass over experiment?
5. How will you detect the presence of intermediates?
6. Why hammett equation is known asLFErelationship?
7. Write down Hammet equation?
8. Write downTafth equation?
9. Give the significance of σ
10. Give thed significance of ρ

5 Marks

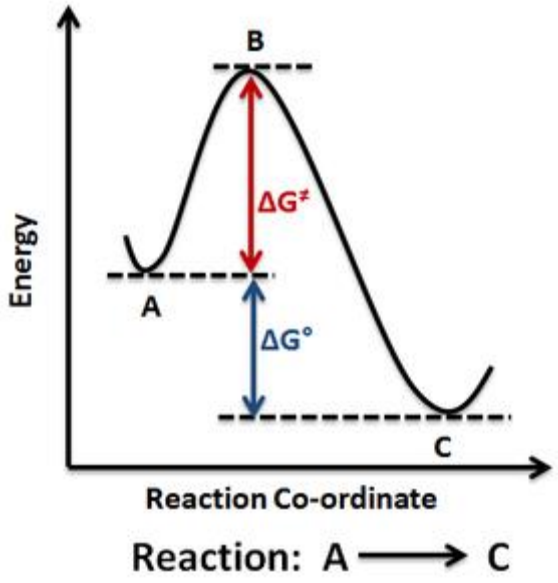
11. Explain Kinetic isotopic effects?
12. Explain wrapping testing and detection of intermediates?
13. Explain isotopic labelling?
14. Explain : Cross over experiment.

10 Marks

15. Write the brief explanation of hammett equation?
16. Explain the following 1.Taft equation2. Kinetic isotopic effects

Energy profile

For a chemical reaction or process an energy profile (or reaction coordinate diagram) is a theoretical representation of a single energetic pathway, along the reaction coordinate, as the reactants are transformed into products. Reaction coordinate diagrams are derived from the corresponding potential energy surface (PES), which are used in computational chemistry to model chemical reactions by relating the energy of a molecule(s) to its structure (within the Born–Oppenheimer approximation). The reaction coordinate is a parametric curve that follows the pathway of a reaction and indicates the progress of a reaction.



Qualitatively the reaction coordinate diagrams (one-dimensional energy surfaces) have numerous applications. Chemists use reaction coordinate diagrams as both an analytical and pedagogical aid for rationalizing and illustrating kinetic and thermodynamic events. The purpose of energy profiles and surfaces is to provide a qualitative representation of how potential energy varies with molecular motion for a given reaction or process.

Potential energy surfaces

In simplest terms, a potential energy surface or PES is a mathematical or graphical representation of the relation between energy of a molecule and its geometry. The methods for describing the potential energy are broken down into a classical mechanics interpretation (molecular mechanics)

and a quantum mechanical interpretation. In the quantum mechanical interpretation an exact expression for energy can be obtained for any molecule derived from quantum principles (although an infinite basis set may be required) but ab initio calculations/methods will often use approximations to reduce computational cost.Molecular mechanics is empirically based and potential energy is described as a function of component terms that correspond to individual potential functions such as torsion, stretches,bends, Van der Waalsenergies,electrostatics and cross terms.Each component potential function is fit to experimental data or properties predicted by initio calculations. Molecular mechanics is useful in predicting equilibrium geometries and transition states as well as relative conformational stability. As a reaction occurs the atoms of the molecules involved will generally undergo some change in spatial orientation through internal motion as well as its electronic environment. Distortions in the geometric parameters result in a deviation from the equilibrium geometry (local energy minima). These changes in geometry of a molecule or interactions between molecules are dynamic processes which call for understanding all the forces operating within the system. Since these forces can be mathematically derived as first derivative of potential energy with respect to a displacement, it makes sense to map the potential energy E of the system as a function of geometric parameters q_1, q_2, q_3 and so on. The potential energy at given values of the geometric parameters (q_1, q_2,…, q_n) is represented as a hyper-surface (when n >2 or a surface when n ≤ 2). Mathematically, it can be written as-

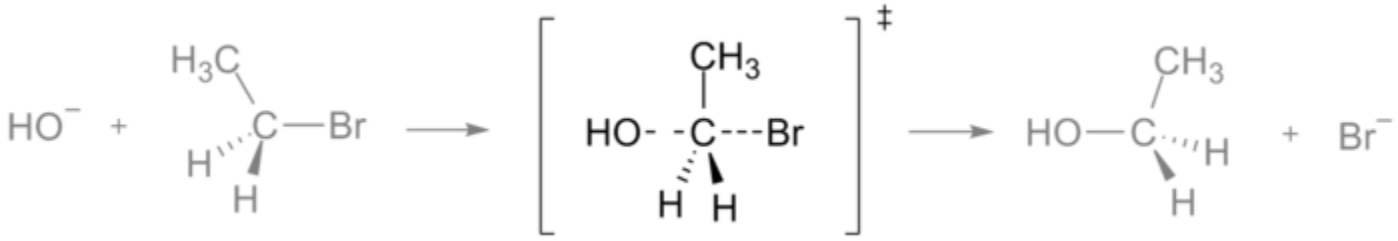
$$\mathbf{E= f(q_1, q_2,\ldots, q_n)}$$

For the quantum mechanical interpretation a PES is typically defined within the Born–Oppenheimer approximation (in order to distinguish between nuclear and electronic motion and energy) which states that the nuclei are stationary relative to the electrons. In other words, the approximation allows the kinetic energy of the nuclei (or movement of the nuclei) to be neglected and therefore the nuclei repulsion is a constant value (as static point charges) and is only considered when calculating the total energy of the system. The electronic energy is then taken to depend parametrically on the nuclear coordinates meaning a new electronic energy (E_e)need to be calculated for each corresponding atomic configuration. PES is an important concept in computational chemistry and greatly aids in geometry and transition state optimization.

Transition state

The transition state of a chemical reaction is a particular configuration along the reaction coordinate. It is defined as the state corresponding to the highest potential energy along this reaction coordinate. It is often marked with the double dagger ‡ symbol.

As an example, the transition state shown below occurs during the S_N2 reaction of bromoethane with a hydroxyl anion:



The activated complex of a reaction can refer to either the transition state or to other states along the reaction coordinate between reactants and products, especially those close to the transition state.According to the transition state theory, once the reactants have passed through the transition state configuration, they always continue to form products.

Product analysis

Product analysis involves examining product features, costs, availability, quality, appearance and other aspects. Product analysis is conducted by potential buyers, by product managers attempting to understand competitors and by third party reviewers.Product analysis can also be used as part of product design to convert a high-level product description into project deliverables and requirements. It involves all facts of the product, its purpose, its operation, and its characteristics.

Reaction intermediate

An **intermediate** is a molecular entity that is formed from the reactants (or preceding intermediates) and reacts further to give the directly observed products of a chemical reaction. Most chemical reactions are stepwise, that is they take more than one elementary step to complete. An intermediate is the reaction product of each of these steps, except for the last one, which forms the final product. Reactive intermediates are usually short lived and are very seldom isolated. Also, owing to the short lifetime, they do not remain in the product mixture.

For example, consider this hypothetical stepwise reaction:

$$A + B \rightarrow C + D$$

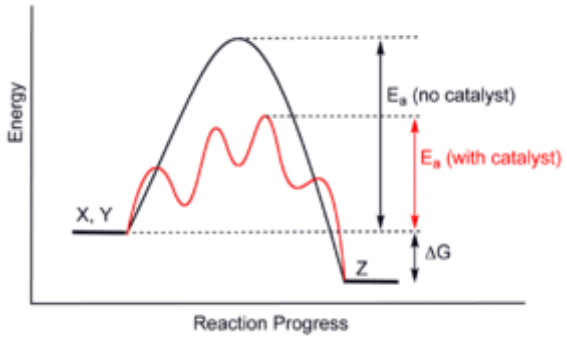
The reaction includes these elementary steps:

$$A + B \rightarrow X^*$$

$$X^* \rightarrow C + D$$

The chemical species X* is an intermediate.

Reaction energetics



Generic potential energy diagram showing the effect of a catalyst in a hypothetical exothermic chemical reaction X + Y to give Z. The presence of the catalyst opens a different reaction pathway (shown in red) with a lower activation energy. The final result and the overall thermodynamics are the same.

Catalysts work by providing an (alternative) mechanism involving a different transition stateand lower activation energy. Consequently, more molecular collisions have the energy needed to reach the transition state. Hence, catalysts can enable reactions that would otherwise be blocked or slowed by a kinetic barrier. The catalyst may increase reaction rate or selectivity, or enable the reaction at lower temperatures. This effect can be illustrated with an energy profile diagram.

In the catalyzed elementary reaction, catalysts do not change the extent of a reaction: they have **no** effect on the chemical equilibrium of a reaction because the rate of both the forward and the reverse reaction are both affected. The second law of thermodynamics describes why a catalyst does not change the chemical equilibrium of a reaction. Suppose there was such a catalyst that shifted an equilibrium. Introducing the catalyst to the system would result in a reaction to move to the new equilibrium, producing energy. Production of energy is a necessary result since reactions are spontaneous only if Gibbs free energy is produced, and if there is no energy barrier, there is no need for a catalyst. Then, removing the catalyst would also result in reaction, producing energy;

i.e. the addition and its reverse process, removal, would both produce energy. Thus, a catalyst that could change the equilibrium would be a perpetual motion machine, a contradiction to the laws of thermodynamics. Thus, catalyst **does not** alter the equilibrium constant. (A catalyst can however change the equilibrium concentrations by reacting in a subsequent step. It is then consumed as the reaction proceeds, and thus it is also a reactant. Illustrative is the base-catalysed hydrolysis of esters, where the produced carboxylic acid immediately reacts with the base catalyst and thus the reaction equilibrium is shifted towards hydrolysis.)

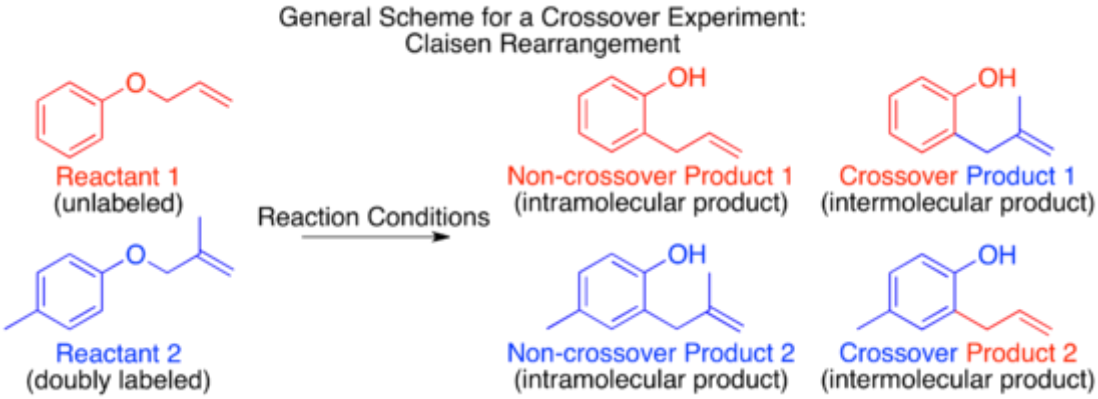
The catalyst stabilizes the transition state more than it stabilizes the starting material. It decreases the kinetic barrier by decreasing the *difference* in energy between starting material and transition state. It does not change the energy difference between starting materials and products (thermodynamic barrier), or the available energy (this is provided by the environment as heat or light).

Crossover Experiment

In chemistry, a **crossover experiment** is a method used to study the mechanism of a chemical reaction. In a crossover experiment, two similar but distinguishable reactants simultaneously undergo a reaction as part of the same reaction mixture. The products formed will either correspond directly to one of the two reactants (non-crossover products) or will include components of both reactants (crossover products). The aim of a crossover experiment is to determine whether or not a reaction process involves a stage where the components of each reactant have an opportunity to exchange with each other.

The results of crossover experiments are often straightforward to analyze, making them one of the most useful and most frequently applied methods of mechanistic study. In organic chemistry crossover experiments are most often used to distinguish between intramolecular and intermolecular reactions.Inorganic and organometallic chemists rely heavily on crossover experiments, and in particular isotopic labeling experiments, for support or contradiction of proposed mechanisms. When the mechanism being investigated is more complicated than an intra- or intermolecular substitution or rearrangement, crossover experiment design can itself become a challenging question. A well-designed crossover experiment can lead to conclusions about a mechanism that would otherwise be impossible to make. Many mechanistic studies include both crossover experiments and measurements of rate and kinetic isotope effects.

Theory



The concept underlying the crossover experiment is a basic one: provided that the labeling method chosen does not affect the way a reaction proceeds, a shift in the labeling as observed in the products can be attributed to the reaction mechanism. The most important limitation in crossover experiment design is therefore that the labeling not affect the reaction mechanism itself.

It can be difficult to know whether or not the changes made to reactants for a crossover experiment will affect the mechanism by which the reaction proceeds. This is particularly true since the aim of the crossover experiment is to provide insight into the mechanism that would allow these types of predictions. There is always the possibility that a label will alter the course of the reaction.

In practice, crossover experiments aim to use the least change possible between the usual conditions of the reaction being studied and the conditions of the crossover experiment. This principle favors isotopic labeling, since changing the isotope of one atom in a molecule is the smallest change that can be both easily enacted and traced in the reaction. If the isotope is placed in the molecule at a position directly involved in the mechanism of the reaction, a kinetic isotope effect is expected. This can be used to study aspects of the mechanism independently or alongside a crossover experiment. The kinetic isotope effect is a change in the rate of reaction based on the change in isotope, not a change in the mechanism of the reaction itself, so isotopic labeling generally satisfies the requirements for a valid crossover experiment. In crossover experiments that do not use isotopic labeling, addition or subtraction of a methyl substituent at a position not involved in any proposed mechanism for the reaction is typically expected to give a valid crossover experiment.

Hammett equation

The Hammett equation in organic chemistrydescribes a linear free-energy relationship prelating reaction rates and equilibrium constants for many reactions involving benzoic acidderivatives with meta- and para-substituents to each other with just two parameters: a substituent constant and a reaction constant. This equation was developed and published by Louis Plack Hammett in 1937 as a follow-up to qualitative observations in a 1935 publication.

The basic idea is that for any two reactions with two aromatic reactants only differing in the type of substituent, the change in free energy of activation is proportional to the change in Gibbs free energy. This notion does not follow from elemental thermochemistry or chemical kinetics and was introduced by Hammett intuitively.

The basic equation

$$\log(K/K_0) = \sigma\rho$$

relating the equilibrium constant, K, for a given equilibrium reaction with substituent R and the reference K_0 constant when R is a hydrogen atom to the substituent constant σ which depends only on the specific substituent R and the reaction constant ρ which depends only on the type of reaction but not on the substituent used.

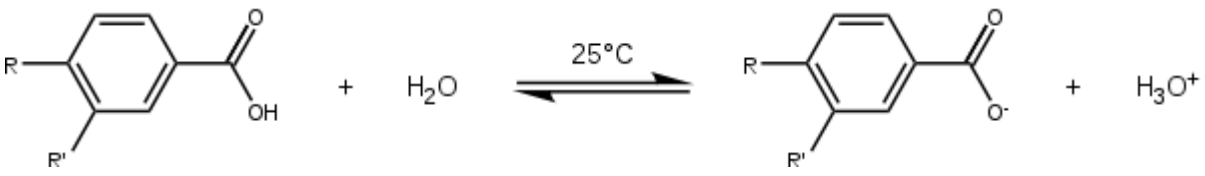
The equation also holds for reaction rates k of a series of reactions with substituted benzene derivatives:

$$\log(k/k_0) = \sigma\rho$$

In this equation k_0 is the reference reaction rate of the unsubstituted reactant, and k that of a substituted reactant.

A plot of $\log(K/K_0)$ for a given equilibrium versus $\log(k/k_0)$ for a given reaction rate with many differently substituted reactants will give a straight line.

The starting point for the collection of the substituent constants is a chemical equilibrium for which both the substituent constant and the reaction constant are arbitrarily set to 1: the ionization of benzoic acid or benzene carboxylic acid (R and R' both H) in water at 25 °C.



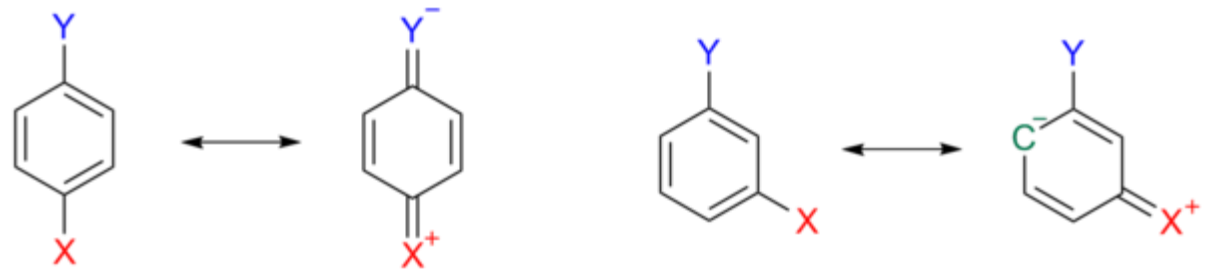
Having obtained a value for K_0, a series of equilibrium constants (K) are now determined based on the same process, but now with variation of the para substituent—for instance, p-hydroxybenzoic acid (R=OH, R'=H) or p-aminobenzoic acid ($R=NH_2$, R'=H). These values, combined in the Hammett equation with K_0 and remembering that $\rho = 1$, give the para substituent constants compiled in

for amine, methoxy, ethoxy, dimethylamino, methyl, fluorine, bromine, chlorine, iodine, nitro an d cyano substituents. Repeating the process with meta-substituents afford the meta substituent constants. This treatment does not include ortho-substituents, which would introduce steric effects.

The σ values displayed in the Table above reveal certain substituent effects. With $\rho = 1$, the group of substituents with increasing positive values—notably cyano and nitro—cause the equilibrium constant to increase compared to the hydrogen reference, meaning that the acidity of the carboxylic acid (depicted on the left of the equation) has increased. These substituents stabilize the negative charge on the carboxylate oxygen atom by an electron-withdrawing inductive effect (-I) and also by a negative mesomeric effect (-M).

The next set of substituents are the halogens, for which the substituent effect is still positive but much more modest. The reason for this is that while the inductive effect is still negative, the mesomeric effect is positive, causing partial cancellation. The data also show that for these substituents, the meta effect is much larger than the para effect, due to the fact that the mesomeric effect is greatly reduced in a meta substituent. With meta substituents a carbon atom bearing the negative charge is further away from the carboxylic acid group (structure 2b).

This effect is depicted in *scheme 3*, where, in a para substituted arene 1a, one resonance structure 1b is a quinoid with positive charge on the X substituent, releasing electrons and thus destabilizing the Y substituent. This destabilizing effect is not possible when X has a meta orientation.



Taft equation

The Taft equation is a linear free energy relationship (LFER) used in physical organic chemistry in the study of reaction mechanismsand in the development of quantitative structure–activity relationships for organic compounds. It was developed by Robert W. Taftin 1952 as a modification to the Hammett equation. While the Hammett equation accounts for how field, inductive, and resonance effects influence reaction rates, the Taft equation also describes the steric effects of a substituent. The Taft equation is written as:

$$\log(k_s/k_{CH3}) = \sigma^*\rho^* + \delta E_s$$

where $\log(k_s/k_{CH3})$ is the ratio of the rate of the substituted reaction compared to the reference reaction, ρ^* is the sensitivity factor for the reaction to polar effects, σ^* is the polar substituent constant that describes the field and inductive effects of the substituent, δ is the sensitivity factor for the reaction to steric effects, and E_s is the steric substituent constant.

UNIT – III

Aliphatic Nucleophilic Substitution

&

Aliphatic Electrophilic Substitution

2 Marks

1. What is aliphatic nucleophilic substitution reaction?
2. What undergoes nucleophilic substitution exclusively by S_N1?
3. What is the order of kinetic in the S_N1 mechanism?

4. What is a nucleophile? Give an example.
5. What is ambident group? Give two examples.
6. Define : Electrophile give an example.
7. What is wurtz reaction? Give an example.
8. What are the factors affecting E_1 and E_2 reaction.
9. What are the difference between S_N1 and S_N2 reaction.
10. What is an aliphatic electrophilic substitution reaction? Give an example.

5 Marks

11. Write the mechanism of Finkelstein reaction..
12. Explain about Williamson's synthesis.
13. Write the mechanism of Friedel Craft reaction.
14. Discuss the mechanism of S_E1.
15. Write the mechanism of Stark – Enamine reaction.

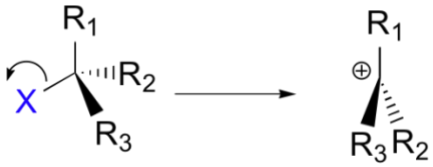
10 Marks

16. Discuss the effect of Aliphatic Nucleophilic Substitution reaction.
17. Write the following mechanism (i) S_N1 (ii) S_E2
18. Write the mechanism of S_N2 and Wurtz reaction.

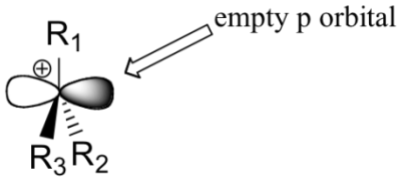
Aliphatic Nucleophilic Sustitutions

S_N1 mechanism

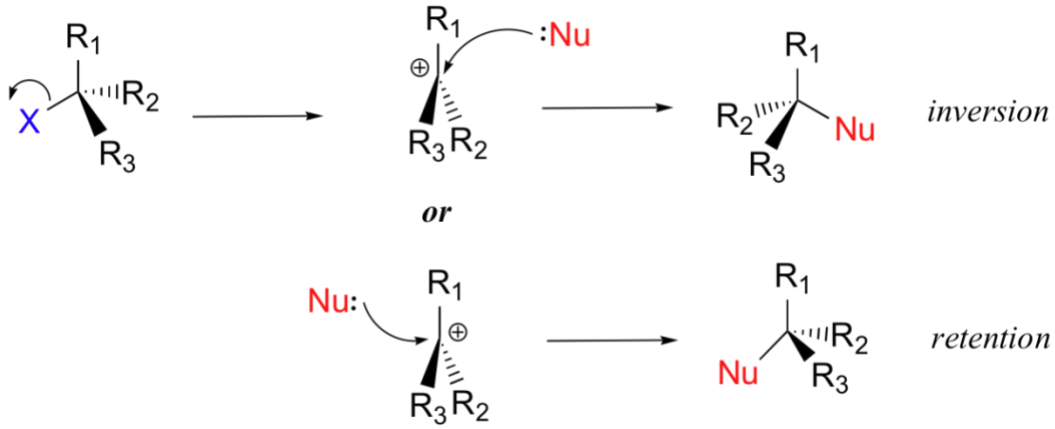
A second model for a nucleophilic substitution reaction is called the '**dissociative**', or '**S_N1**' mechanism: in this picture, the C-X bond breaks *first*, before the nucleophile approaches:



This results in the formation of a carbocation: because the central carbon has only three bonds, it bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized *p* orbital.

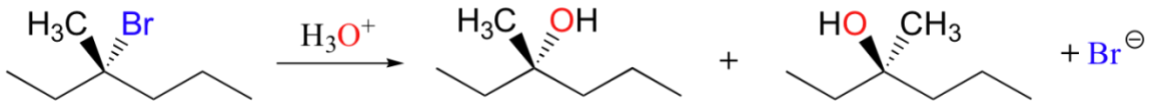


In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry.



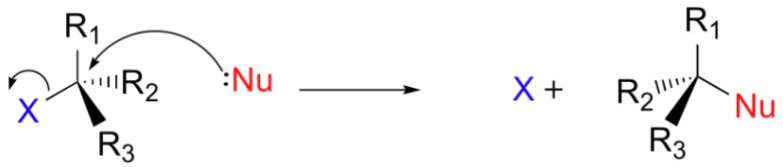
We saw that S_N2 reactions result specifically in inversion of stereochemistry at the electrophilic carbon center. What about the stereochemical outcome of S_N1 reactions? In the model S_N1 reaction shown above, the leaving group dissociates completely from the vicinity of the reaction before the nucleophile begins its attack. Because the leaving group is no longer in the picture, the nucleophile is free to attack from either side of the planar, sp^2-hybridized carbocation electrophile. This means that about half the time the product has the same stereochemical configuration as the starting material (retention of configuration), and about half the time the stereochemistry has been inverted. In other words, *racemization* has occurred at the carbon center. As an example, the tertiary alkyl

bromide below would be expected to form a racemic mix of *R* and *S* alcohols after an S_N1 reaction with water as the incoming nucleophile.



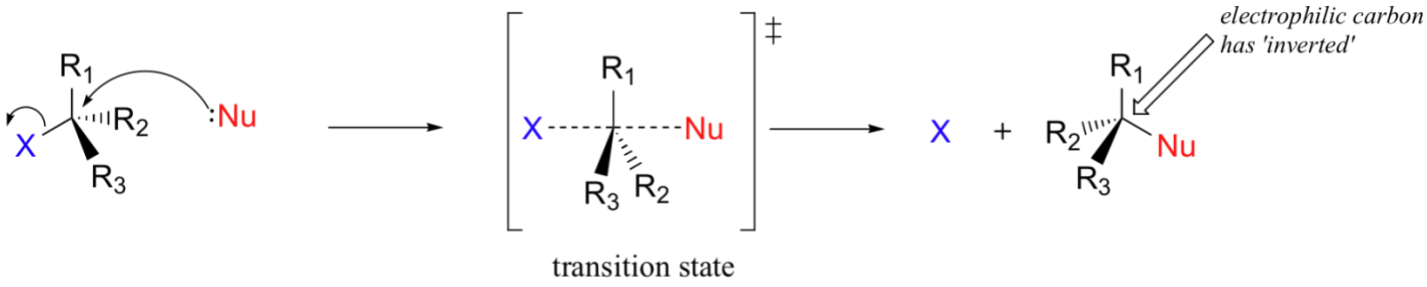
S_N2 mechanism

There are two mechanistic models for how an alkyl halide can undergo nucleophilic substitution. In the first picture, the reaction takes place in a single step, and bond-forming and bond-breaking occur simultaneously. (In all figures in this section, 'X' indicates a halogen substituent).



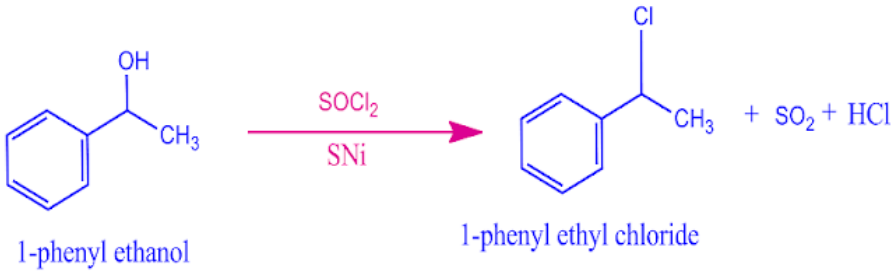
This is called an '**S_N2**' mechanism. In the term S_N2, S stands for 'substitution', the subscript Nu stands for 'nucleophilic', and the number 2 refers to the fact that this is a **bimolecular reaction**. The nucleophile, being an electron-rich species, must attack the electrophilic carbon from the *back side* relative to the location of the leaving group. Approach from the front side simply doesn't work: the leaving group - which is also an electron-rich group - blocks the way.

The result of this backside attack is that the stereochemical configuration at the central carbon *inverts* as the reaction proceeds. In a sense, the molecule is turned inside out. At the transition state, the electrophilic carbon and the three 'R' substituents all lie on the same plane.



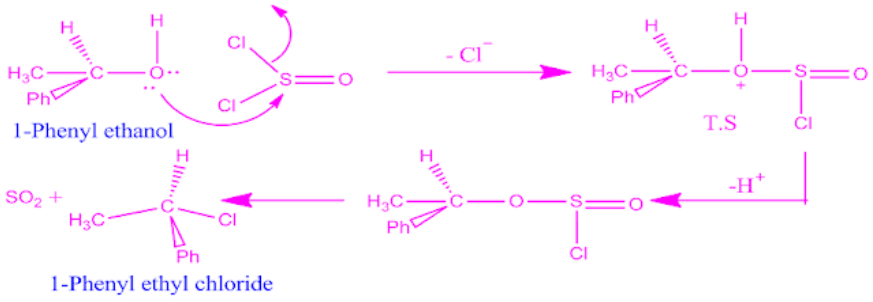
S_Ni Reaction Mechanism

The term SNi stands for substitution nucleophilic internal. In SN1 and SN2 reaction mechanism, the racemization and inversion of the configuration of the product take place. But Hughes, Ingold has shown that optically active 1-phenyl ethanol reacts with thionyl chloride to give 1-phenyl ethyl chloride with complete retention of configuration.Normally the product should be inversion of configuration. so former can be explained by internal mechanism which is called SNi mechanism.



Mechanism

The solvents used in SNi reaction is diethyl ether or tetra hydro furan. The mechanism of SNi reaction shown below.

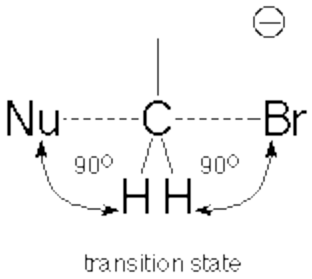


Factors Affecting The S_N2 Reaction

Electrophile

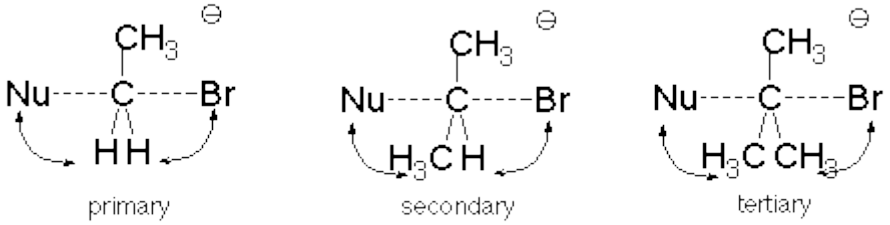
(a) Structure of the alkyl group

In the structure of the S_N2 transition state, there are 90° bond angles between the breaking bond to the leaving group and the three bonds which remain connected to the carbon as well as between the bond being made to the nucleophile and those same three bonds.



transition state

As long as the two of the groups attached to the carbon being attacked are small hydrogens, the repulsions which happen do not require much energy. If the groups attached to the carbon are larger, though, like methyl groups, the transition state energy increases, the activation energy increases, and the reaction becomes much slower.



primary secondary tertiary

transition states

This means that the reactivity order for alkyl halides in S_N2 reactions is:

methyl > primary > secondary > tertiary

The practical outcome of this is that S_N2 reactions are generally reliable only when the alkyl halide is primary, though under the correct conditions secondary halides can react well also.

(b) Leaving group ability – what makes a good leaving group?

In our general discussion of nucleophilic substitution reactions, we have until now been designating the leaving group simply as "X". As you may imagine, however, the nature of the leaving group is an important consideration: if the C-X bond does not break, the new bond between the nucleophile and electrophilic carbon cannot form, regardless of whether the substitution is S_N1 or S_N2. There are two main factors: The strength of the C-X bond, and the stability of the X group after it has left. It turns out that the two factors lead to the same prediction for halogen leaving group ability:

$$I > Br > Cl > F$$

C-X bond strength

Since the bond between the carbon and the leaving group is being broken in the transition state, the weaker this bond is the lower the activation energy and the faster the reaction. This leads to the following reactivity order for alkyl halides

$$R{-}I > R{-}Br > R{-}Cl > R{-}F$$

Practically, alkyl fluorides are not used for S_N2 reactions because the C-F bond is too strong. Often alkyl iodides are reactive enough to be difficult to store, so the the common choices for reactions are alkyl chlorides and alkyl bromides.

Stability of the group after leaving

When the C-X bond breaks in a nucleophilic substitution, the pair of electrons in the bond goes with the leaving group. In this way, the leaving group is analogous to the conjugate base in a Brønsted-Lowry acid-base reaction. When we were evaluating the strength of acids in chapter 7, what we were really doing was evaluating the stability of the conjugate base that resulted from the proton transfer. All of the concepts that we used to evaluate the stability of conjugate bases we can use again to evaluate leaving groups. In other words, the trends in basicity are parallel to the trends in leaving group potential – the weaker the base, the better the leaving group. Just as with

conjugate bases, the most important question regarding leaving groups is this: when a leaving group leaves and takes a pair of electrons with it, how well is the extra electron density stabilized?

In laboratory synthesis reactions, halides often act as leaving groups. Iodide, which is the *least* basic of the four main halides, is also the *best* leaving group – it is the most stable as a negative ion. Fluoride is the least effective leaving group among the halides, because fluoride anion is the most basic.

We already know that the use of polar, aprotic solvents increases the reactivity of nucleophiles in S_N2 reactions, because these solvents do not 'cage' the nucleophile and keep it from attacking the electrophile.

Factors Affecting The S_N1 Reaction

Electrophile

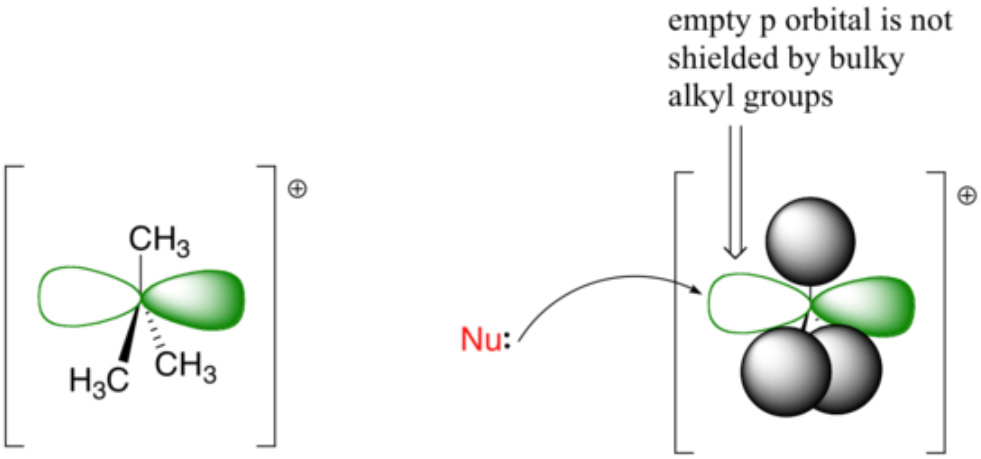
This topic was examined in general in section 6.5., and also considered above for S_N2. But a electrophile that is good for S_N2 is not necessarily good for S_{N1}, for reasons that will become clear. We also have a new factor to consider – the stability of the carbocation that is formed as a result of the heterolysis step.

(a) Structure of the alkyl group

In the vast majority of the nucleophilic substitution reactions you will see in this and other organic chemistry texts, the electrophilic atom is a carbon which is bonded to an electronegative atom, usually oxygen, nitrogen, sulfur, or a halogen. The concept of electrophilicity is relatively simple: an electron-poor atom is an attractive target for something that is electron-rich, *i.e.* a nucleophile. However, we must also consider the effect of steric hindrance on electrophilicity. In addition, we must discuss how the nature of the electrophilic carbon, and more specifically the stability of a potential carbocationic intermediate, influences the S_N1 reaction.

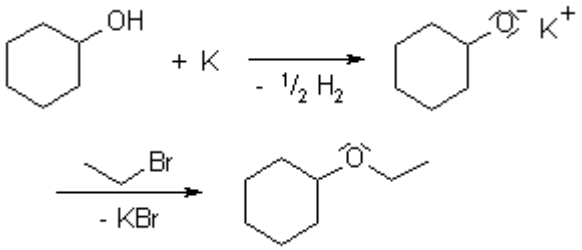
Steric effects on electrophilicity

In an S_N1 mechanism, the nucleophile attacks an sp^2-hybridized carbocation intermediate, which has trigonal planar geometry with 'open' 120 angles.



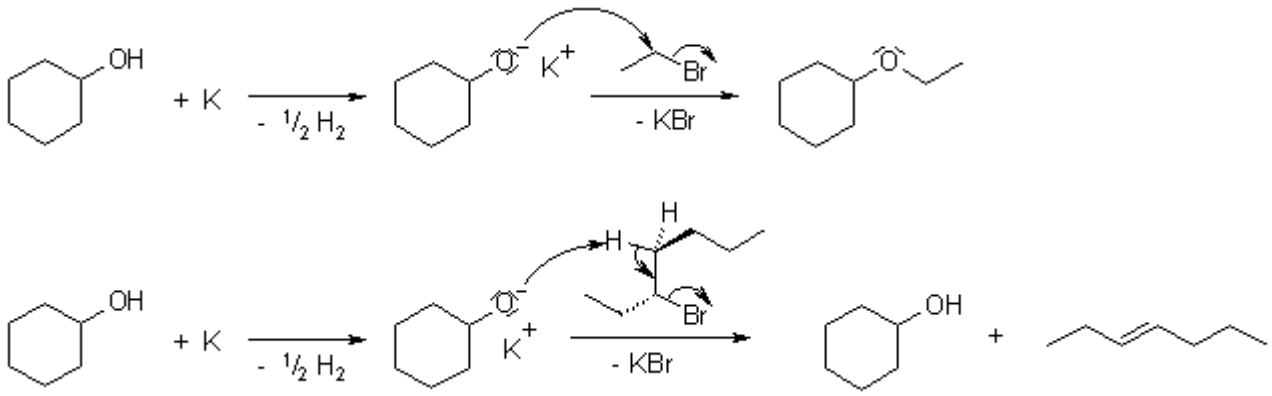
With this open geometry, the empty p orbital of the electrophilic carbocation is no longer significantly shielded from the approaching nucleophile by the bulky alkyl groups. A carbocation is a very potent electrophile, and the nucleophilic step occurs very rapidly compared to the first (ionization) step. This is in direct contrast to the S_N2 reaction, where bulky alkyl groups hinder the reaction.

Williamson Synthesis



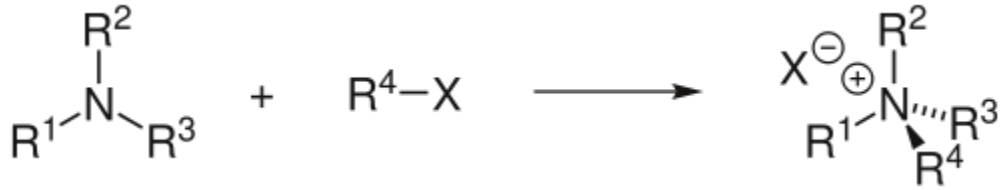
This method is suitable for the preparation of a wide variety of unsymmetric ethers. The nucleophilic substitution of halides with alkoxides leads to the desired products.If the halides are sterically demanding and there are accessible protons in

the β-position, the alkoxide will act as a base, and side products derived from elimination are isolated. **Mechanism**



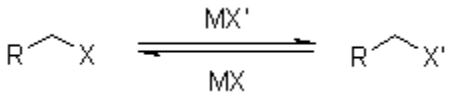
Menshutkin Reaction

The Menshutkin reaction converts a tertiary amine into a quaternary ammonium salt by reaction with an alkyl halide. Similar reactions occur when tertiary phosphines are treated with alkyl halides.

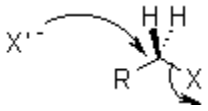


The reaction is the method of choice for the preparation quaternary ammonium salts.Some phase transfer catalysts (PTC) can be prepared according to the Menshutkin reaction, for instance the synthesis of triethyl benzyl ammonium chloride (TEBA) from triethylamine and benzyl chloride:

Finkelstein Reaction

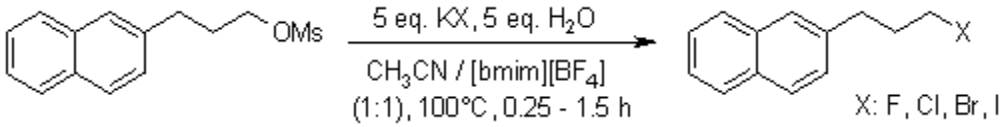


Treatment of a primary alkyl halide or pseudohalide with an alkali metal halide (e.g. KF, KI) leads to replacement of the halogen via an S_N2 Reaction.



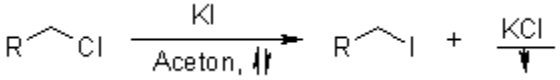
Mechanism

The equilibrium position of the reaction depends on the nucleophilicity of the anion, whether a good leaving group is present, and whether one anion is better stabilized than the other in a given solvent. For example, reactions with KF will thus lead cleanly to fluoroalkanes, because fluoride is such a poor leaving group due to the stability of the C-F bond.

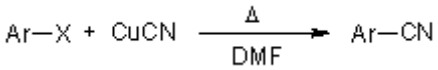


In general, the reaction is run with an excess of the metal halide. The use of metal salts that have a high lattice energy require the addition of a crown ether (compare the reaction times for KF and CsF in the example above).

The equilibrium position of the reaction also depends on the solubility of the metal salt in the solvent used. Thus, the substitution of bromo- and chloroalkanes with KI in acetone leads cleanly to the desired iodoalkane products, since KCl and KBr are insoluble in acetone and are consequently removed from the equilibrium:



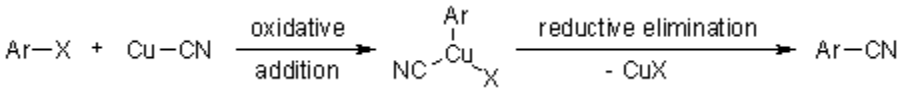
Rosenmund-von Braun Reaction



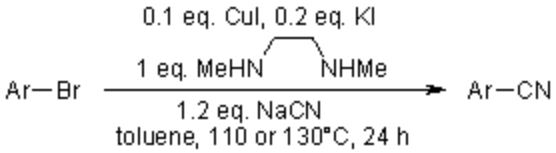
Aryl nitriles can be prepared by the cyanation of aryl halides with an excess of copper(I) cyanide in a polar high-boiling solvent such as DMF, nitrobenzene, or pyridine at reflux temperature.

Mechanism

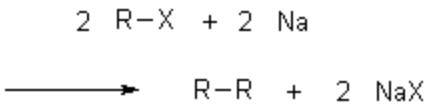
The mechanism probably involves the formation of a Cu(III) species through oxidative addition of the aryl halide. Subsequent reductive elimination then leads to the product:



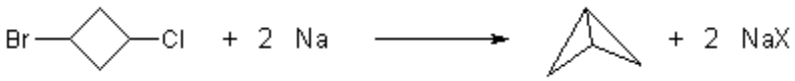
The excess of copper cyanide and the use of a polar, high-boiling point solvent makes the purification of the products difficult. In addition, elevated temperatures (up to 200°C) lower the functional group tolerance. The use of alkali metal cyanides or cyanation reagents such as cyanohydrins, a catalytic amount of copper(I) iodide and kalium iodide, allows a mild, catalytic cyanation of various aryl bromides.



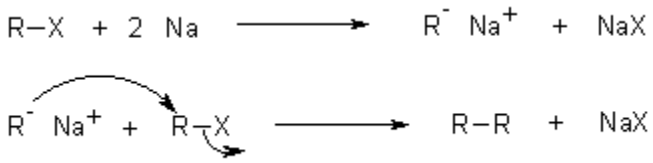
Wurtz Reaction



The Wurtz Coupling is one of the oldest organic reactions, and produces the simple dimer derived from two equivalents of alkyl halide. The intramolecular version of the reaction has also found application in the preparation of strained ring compounds:



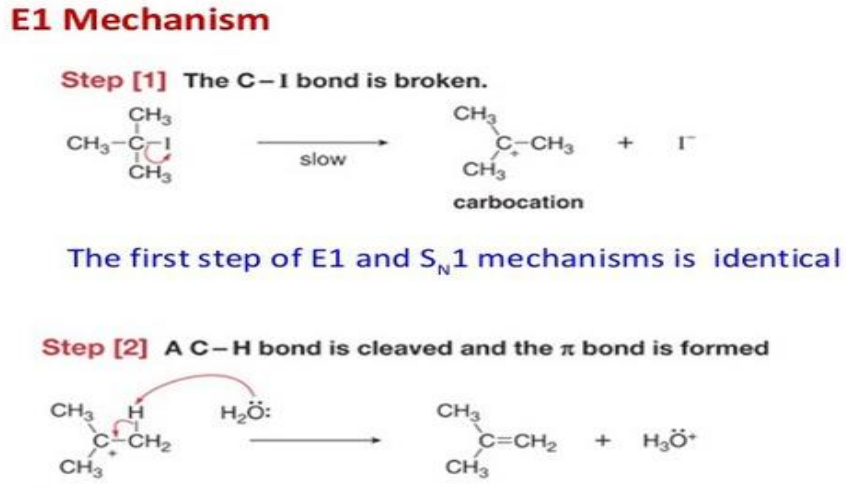
Using two different alkyl halides will lead to an approximately statistical mixture of products. A more selective unsymmetric modification is possible if starting materials have different rates of reactivity. **Mechanism**



Aliphatic Electrophilic Substitution

SE1 mechanism

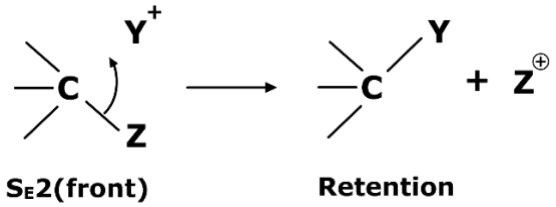
The SE1 mechanism involves two steps: the first step is a slow rate determining ionization step leading to formation of the carbanion. The second step involves fast combination of electrophile resulting in to the products.



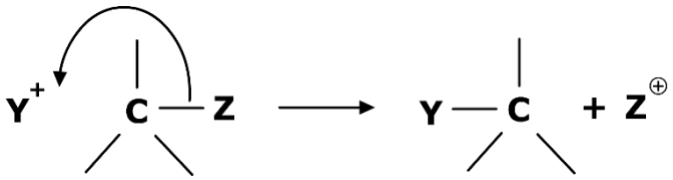
Mechanism of $S_E2$reactions

The S_E2 reaction mechanism proceeds via a single transition state where the old bonds and the newly formed bonds are both present simultaneously. Unlike S_N2 substitution, which always results in inversion of configuration of reaction centre, for S_E2 reactions there are two possible ways of electrophile attack to the reactioncentre.

The first one is attack from the front, which is called S_E2 (front) that results in retention of configuration.



Thesecondoptionisattackoftheelectrophilefromtherear,whichiscalledS_E2(bac k) that leads to inversion ofconfiguration.



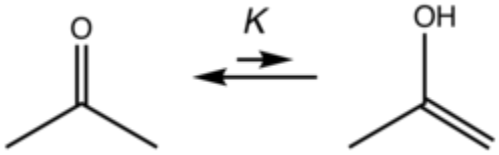
Majority of second-order electrophilic substitutions proceed via retention of configuration implicatingfrontsideattackresultingfromS_E2(front)mechanism.Forexample,whencompound 1 was treated with labeled mercuric chloride*, the product 2 produced with 100% retention ofconfiguration, thereby confirming S_E2 (front)mechanism.

Keto - Enol Tautomerism

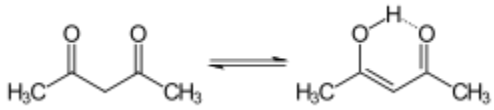
Enols, or more formally, alkenols, are a type of reactive structure or intermediate in organic chemistry that is represented as an alkene (olefin) with a hydroxyl group attached to one end of the alkene double bond. The terms enol and alkenol are portmanteaus deriving from "-ene"/"alkene" and the "-ol" suffix indicating the hydroxyl group of alcohols, dropping the terminal "-e" of the first term. Generation of enols often involves removal of a hydrogen adjacent (α-) to

the carbonyl group—i.e., deprotonation, its removal as a proton, H^+. When this proton is not returned at the end of the stepwise process, the result is an anion termed an enolate. The enolate structures shown are schematic; a more modern representation considers the molecular orbitals that are formed and occupied by electrons in the enolate. Similarly, generation of the enol often is accompanied by "trapping" or masking of the hydroxy group as an ether, such as a silyl enol ether.

Keto-enol examples



Keto-enol equilibrium for acetone.



Ketone tautomerization, keto-form at left, enol at right. Ex. is 2,4-pentanedione, a hydrogen bond (---) stabilized enol.

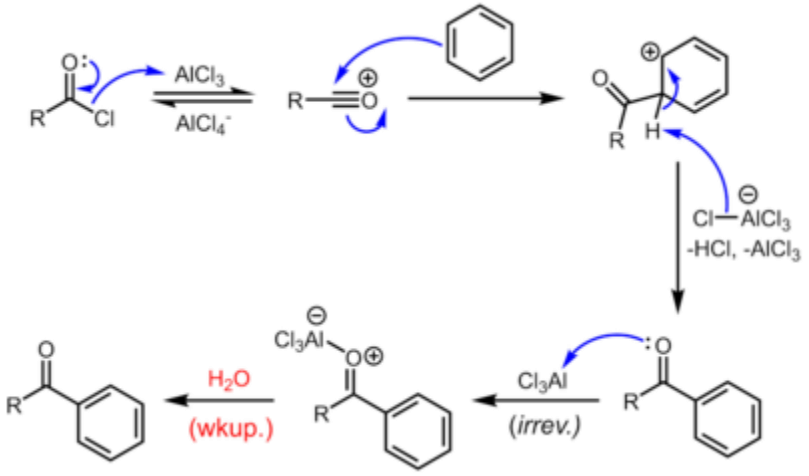
Aldehyde tautomerization, enol-form at left, "keto" at right; Ex. is tartronaldehyde (reductone), an enediol-type of enol.

In organic chemistry, keto–enol tautomerism refers to a chemical equilibrium between a keto form (a ketone or an aldehyde) and an enol (an alcohol). The keto and enol forms are said to be tautomers of each other. The interconversion of the two forms involves the movement of an alpha hydrogen atom and the reorganisation of bonding electrons; hence, the isomerism qualifies as tautomerism.

Friedel – Craft Acylation

The reaction proceeds through generation of an acylium center. The reaction is completed by deprotonation of the arenium ion by $AlCl_4^-$, regenerating the $AlCl_3$ catalyst. However, in contrast to the truly catalytic alkylation reaction, the formed ketone is a moderate Lewis base, which forms

a complex with the strong Lewis acid aluminum trichloride. The formation of this complex is typically irreversible under reaction conditions. Thus, a stochiometric quantity of $AlCl_3$ is needed. The complex is destroyed upon aqueous workup to give the desired ketone. For example, the classical synthesis of deoxybenzoin calls for equivalents of $AlCl_3$ with respect to the limiting reagent, phenylacetyl chloride. In certain cases, generally when the benzene ring is activated, Friedel-Crafts acylation can also be carried out with *catalytic* amounts of a milder Lewis acid (e.g. Zn(II) salts) or a Brønsted acid catalyst using the anhydride or even the carboxylic acid itself as the acylation agent.

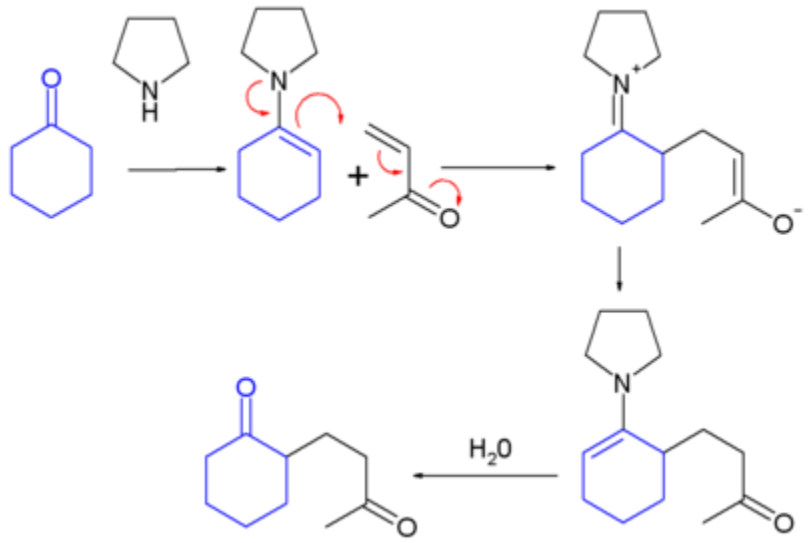


Stark Enamine Reaction

The Stork enamine alkylation, involves the addition of an enamine to a Michael acceptor (e.g, an α,β -unsaturated carbonyl compound) or another electrophilic alkylation reagent to give an alkylated iminium product, which is hydrolyzed by dilute aqueous acid to give the alkylated ketone or aldehyde.[1] Since enamines are generally produced from ketones or aldehydes, this overall process (known as the Stork enamine synthesis) constitutes a selective monoalkylation of a ketone or aldehyde, a process that may be difficult to achieve directly.

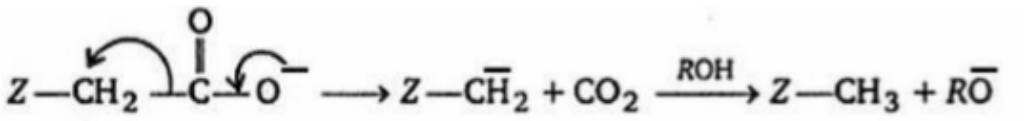
The Stork enamine synthesis:

1. formation of an enamine from a ketone
2. addition of the enamine to an alpha, beta-unsaturated aldehyde or ketone
3. hydrolysis of the enamine back to a ketone



Decarboxylation of aliphatic acids

Aliphatic acids with certain functional groups, such as double or triple bonds at or β position undergo facile decarboxylation. The reaction proceeds via involvement of a carbanion intermediate that subsequently acquires a proton from the solvent or other source. For such reactions loss of CO2 is the rate limiting step. Thus the rate law for the following reaction is, Rate = k[Z-CH2COO-]



Where, Z= COOH, COR, Ar, NO2, CN, CH3

UNIT – IV

Aromatic Nucleophilic Substitution

&

Aromatic Electrophilic Substitution

UNIT- 4

2 Mark Question

1 . What is aromatic nucleophilic substitution? Give one example.

2 . What is cine substitution?

3. Define : ipso substitution.

4, What is Ziegler alkylation?

5 . Write the Hammett equation.

5 Mark Question

6 . Discuss about the SN1 Reaction and mechanism.

7. Write notes on Benzyne mechanism.

8. Discuss about the reaction and mechanism of Von-ritcher reaction.

9. Discuss about the orgin of Hammet equation.

10. Describe the Arenium ion mechanism.

10 mark Question

11. Detailed account an factors affecting the aromatic Nucleophilic substitution.

12. Discuss about the orientation and reactivity of Arenium ion mechanism.

Nucleophilic Aromatic Substitution

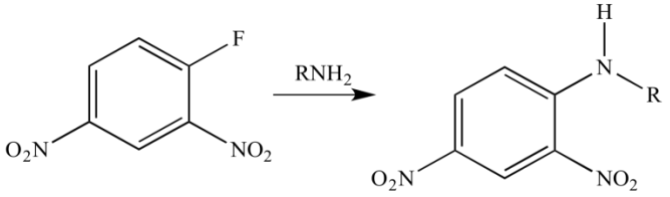
The replacement of substituent in an aromatic compound by a nucleophile is called aromatic nucleophilic substitution.

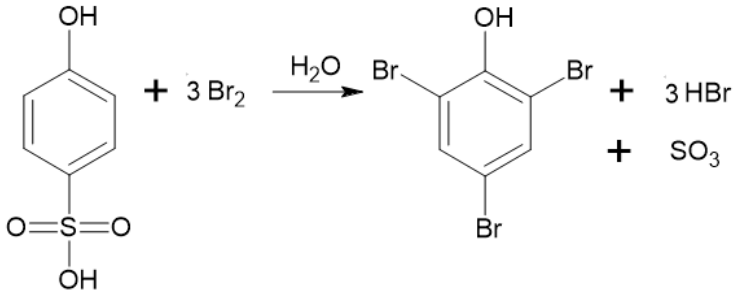
$$C_6H_5cl + NaoH \Longrightarrow C_6H_5OH + Nacl$$

Ipso Attack

The attachment of an entering group to a position in an aromatic compound already carrying a substituent group (other than hydrogen). The entering group may displace that substituent group but may also itself be expelled or migrate to another position in a subsequent step.

Ipso substitution: **Substitution** of an aromatic ring substituent (i.e., an attachment other than hydrogen). The mechanism is usually nucleophilic aromatic **substitution**, but **ipso substitution** by an electrophilic aromatic **substitution** mechanism is also possible.



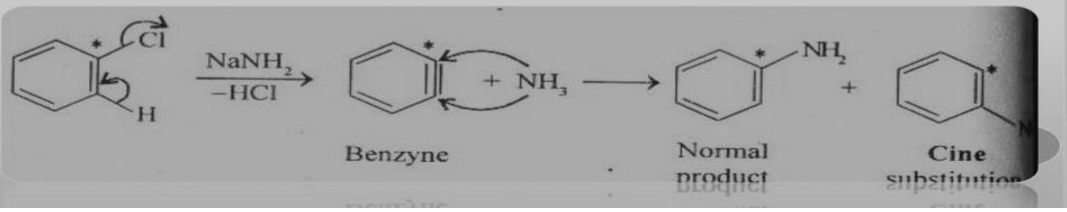


Cine – Substitution :-

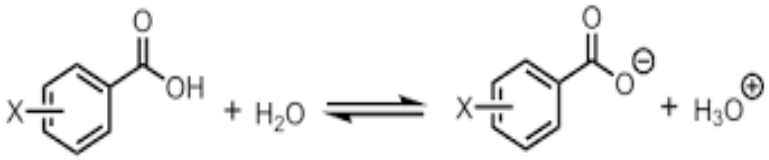
In normal aromatic nucleophilic substitution reactions, substitution of group takes place the position of leaving group.

But in cine substitution, substitution of group takes place also at adjecent position of leaving group. This is possible only when benzyne intermediate is formed.

It can be proved by isotopic labelling of C14.



Hammet equation



$$\log\left(\frac{k}{k_H}\right) = s\,r \quad \text{or} \quad \log\left(\frac{K}{K_H}\right) = s\,r$$

s = substituent constant
r = reaction constant

Factors affecting the Aromatic nucleophilic substitution

The attachment of an entering group to a position in an aromatic compound already carrying a substituent group (other than hydrogen). The entering group may displace that substituent group but may also itself be expelled or migrate to another position in a subsequent step.reaction

- he **aromatic ring acts as a nucleophile**, and attacks an added electrophile E
- An **electron-deficient carbocation intermediate is formed** (the rate-determining step) which is then deprotonated to restore aromaticity

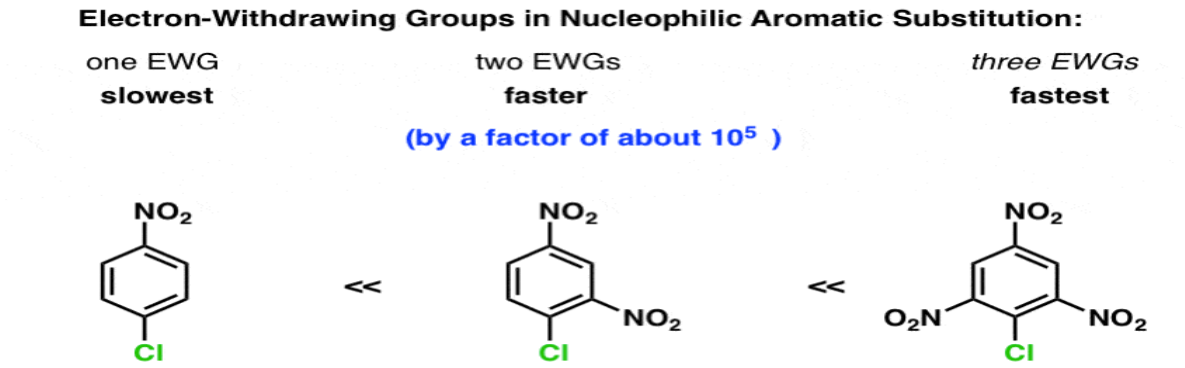
- **electron-donating groups on the aromatic ring** (such as OH, OCH_3, and alkyl) **make the reaction faster**, since they help to stabilize the electron-poor carbocation intermediate
- **Lewis acids can make electrophiles even more electron-poor** (reactive), increasing the reaction rate. For example $FeBr_3$ / Br_2 allows bromination to occur at a useful rate on benzene, whereas Br_2 by itself is slow).

Everything we've learned so far about substitution on aromatic rings would teach us that it proceeds much faster with methoxybenzene than with nitrobenzene, and much faster with an electrophile like Cl_2 than with, say, an electron-rich nucleophile like $NaOCH_3$.

Which brings us to the reaction below. The aromatic ring is electron-poor and we're adding an electron-rich nucleophile.

The Effect Of Substituents

In nucleophilic aromatic substitution (NAS), all the trends you learned in electrophilic aromatic substitution operate, but *in reverse.* The first trend to understand is that **electron withdrawing groups** (EWG's) dramatically **increase** the rate of reaction, not decrease it. From this, it follows that the more EWG's there are, the faster the reaction. For example, the rate of NAS for 2,4-dinitrophenyl chloride is about 10^5 times faster than for *p*-nitrophenyl chloride. (I don't have a rate constant for 2,4,6-trinitrophenyl chloride readily available, but it is orders of magnitude faster still).



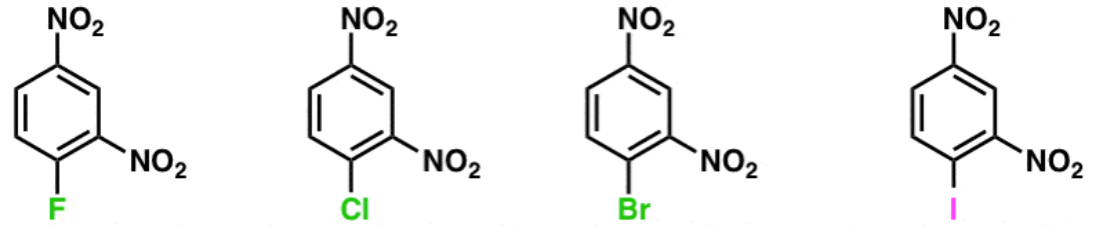
The Effect Of The Leaving Group

One of the most eye-opening aspects of nucleophilic aromatic substitution is noting that fluorine is often used as a leaving group. After all, given the stern tones we instructors use in Org 1 on this subject, the words "FLUORINE IS NEVER A LEAVING GROUP

IN SN2 AND SN1 REACTIONS" may as well have been carved on one of the stone tablets handed down to Moses on Mt. Sinai.

Here's a thought: if even a "bad" leaving group like fluorine works in nucleophilic aromatic substitution, then surely a "better" leaving group like bromine or iodine would work even better. For one reaction studied, F as the leaving group was observed to be 3300 times faster than iodine And between chlorine, bromine, and iodine, the difference was only by a factor of about 3.

Fluorine is actually a better leaving group than Cl, Br, and I



3300	4.3	4.3	1

suggests that C–F bond cleavage is not involved in the rate-determining step!

So what could be different about nucleophilic aromatic substitution that makes the rate of reaction much less sensitive to the identity of the leaving group than the S_N1 and S_N2 reactions.

Well, for one thing, this would suggest that, unlike the S_N1 and S_N2 reactions, C-F bond cleavage does not occur in the rate-determining step. This information is helpful in coming up with a mechanism for the reaction.

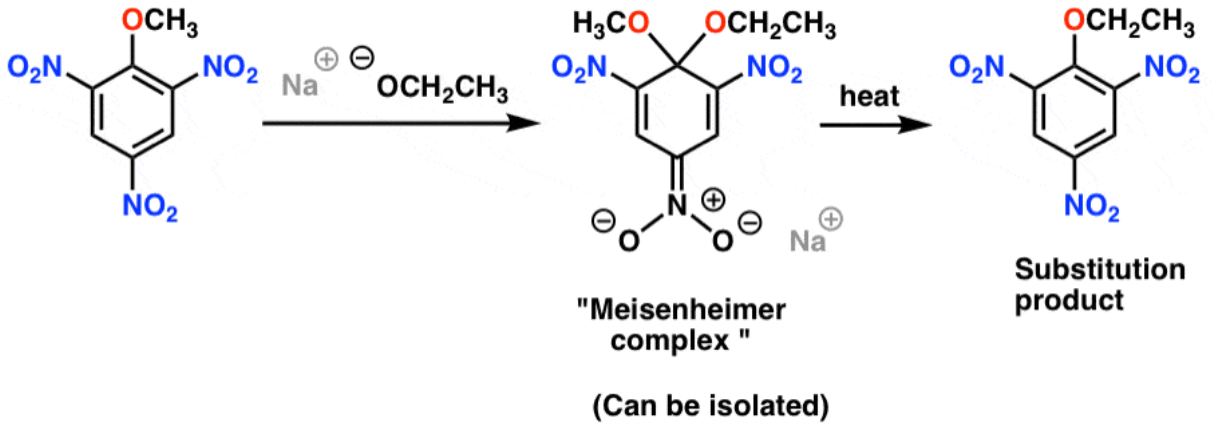
The Effect Of Substitution

Unlike in electrophilic aromatic substitution, there are no "*ortho-*,*para-*" or "*meta-*" directors. The position of substitution is controlled by the placement of the leaving group. However that isn't to say that the rate of the reaction isn't affected by the relative position of the leaving group and the electron-withdrawing group. For example, nucleophilic aromatic substitution of *p*-nitrophenyl fluoride is orders of magnitude faster than *m*-nitrophenyl fluoride, even though the NO2 is closer to the leaving group and should

presumably exert more of an inductive effect. The *ortho* isomer is also faster than the *meta* by a large margin.

The "Meisenheimer" Intermediate

Intermediates from nucleophilic aromatic substitution (called "Meisenheimer complexes" after their 1902 discovery) have been isolated.
Further heating of these products results in the substitution product.

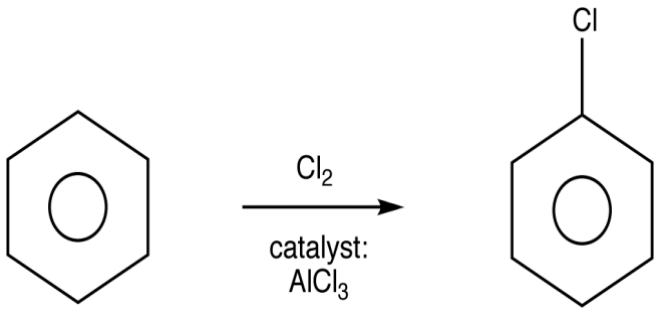


Pretty clear evidence for a two-step mechanism that proceeds through
1) attack of nucleophile on the ring
2) elimination of the leaving group

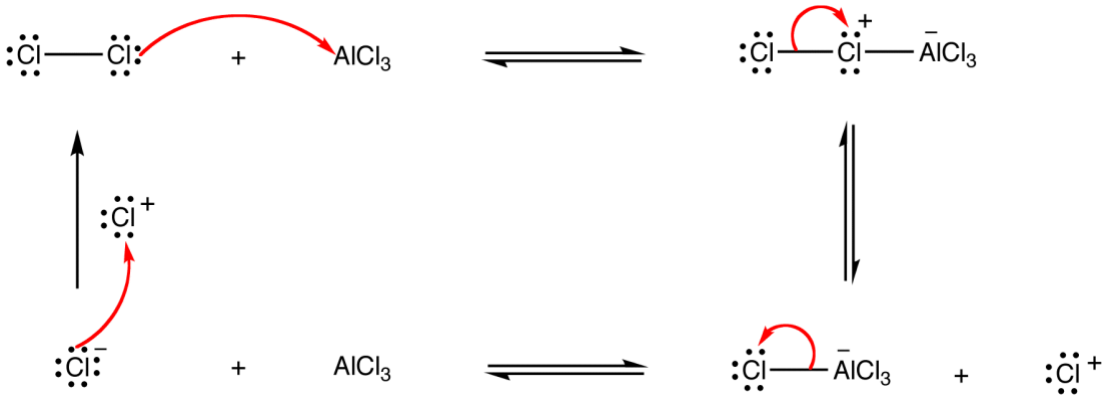
Meisenheimer intermediates can be isolated and characterized. However, if heated, the compound goes on to form the final nucleophilic aromatic substitution product

Arenioum ion mechanism

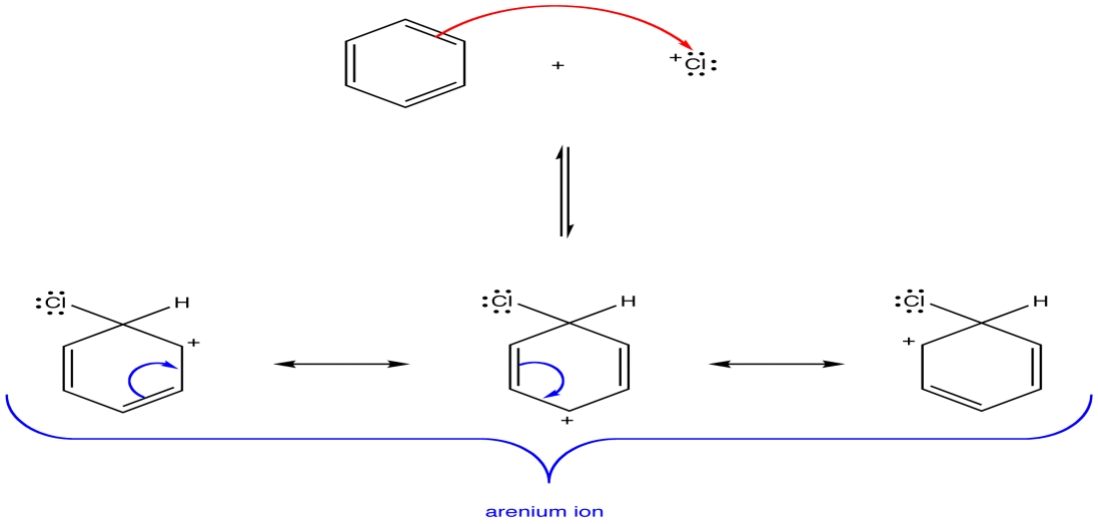
resonance-stabilized carbocation intermediate of electrophilic aromatic substitution of arenes is called the arenium ion. eg:



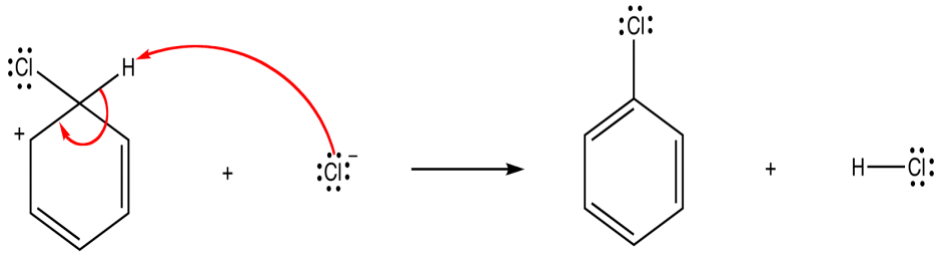
Mechanism:



Step 1



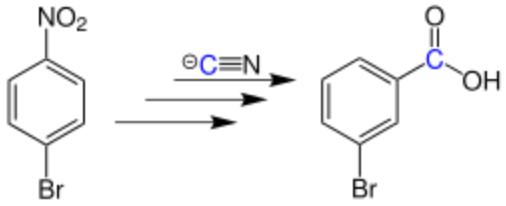
Step 2:



Von Richter reaction.

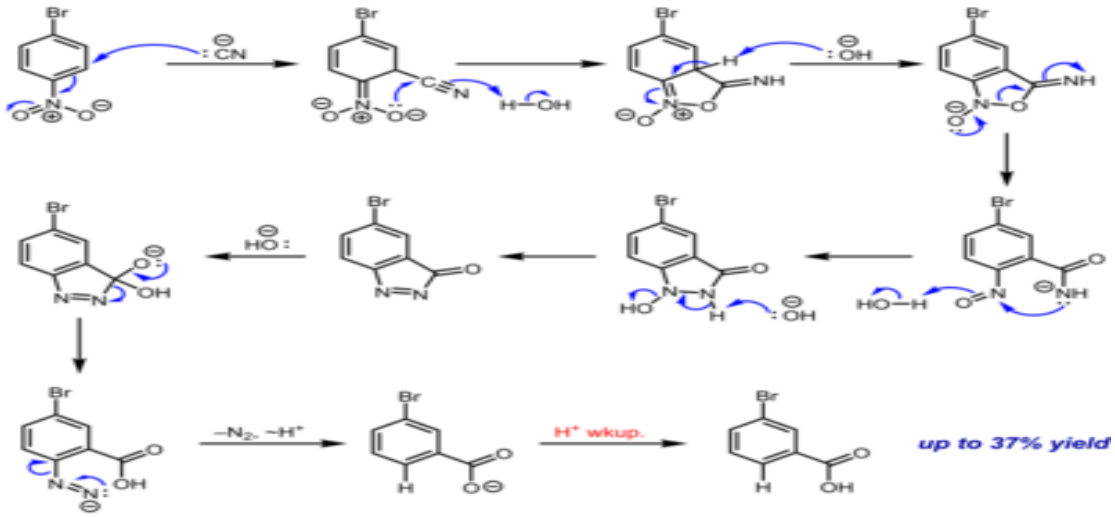
It is the reaction of aromatic nitro compounds with potassium cyanide in aqueous ethanol to give the product of *cine* substitution (ring substitution resulting in the entering group positioned adjacent to the previous location of the leaving group) by a carboxyl group. Although it is not generally synthetically useful due to the low chemical yield and formation of numerous side products

The reaction below shows the classic example of the conversion of *p*-bromonitrobenzene into *m*-bromobenzoic acid.



The reaction is a type of nucleophilic aromatic substitution. Besides the bromo derivative, chlorine- and iodine-substituted nitroarenes, as well as more highly substituted derivatives, could also be used as substrates of this reaction. However, yields are generally poor to moderate, with reported percentage yields ranging from 1% to 50%.

Reaction Mechanism



First, the cyanide attacks the carbon *ortho* to the nitro group. This is followed by ring closing via nucleophilic attack on the cyano group, after which the imidate intermediate is rearomatized. Ring opening via nitrogen–oxygen bond cleavage gives an *ortho*-nitroso benzamide, which recyclizes to give a compound containing a nitrogen–nitrogen bond. Elimination of water gives a cyclic azoketone, which undergoes nucleophilic attack by hydroxide to give a tetrahedral intermediate.

This intermediate collapses with elimination of the azo group to yield an aryldiazene with an *ortho* carboxylate group, which extrudes nitrogen gas to afford the anionic form of the observed benzoic acid product, presumably through the generation and immediate protonation of an aryl anion intermediate. The product is isolated upon acidic workup. Subsequent mechanistic studies have shown that the subjection of independently prepared *ortho*-nitroso benzamide and azoketone intermediates to von Richter reaction conditions afforded the expected product, lending further support to this proposal.

Orientation and reactivity of Arenium ion mechanism.

planning syntheses based on substitution reactions of substituted benzenes, it is imperative to be able to predict in advance which of the available positions of the ring are likely to be most reactive. This is now possible with a rather high degree of certainty, thanks to the work of many chemists during the past 100 years. Few, if any, other problems in organic chemistry have received so much attention over so many years, and there are now sufficient data on the orientation and reactivity effects of ring substituents in electrophilic substitution to permit the formation of some very valuable generalizations.

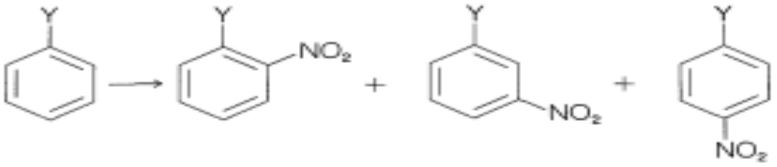
Basically, three experimental problems are involved in the substitution reactions of aromatic compounds: (1) proof of structure of the isomers that are formed; (2)

determination of the percentage of each isomer formed, if the product is a mixture; and (3) measurement of the reactivity of the compound being substituted relative to some standard substance, usually benzene. For benzenoid compounds, structures can be established by the historically important substitution method or with the aid of correlations between spectroscopic properties and positions of substitution. Also, it is often possible to identify the isomers by converting them to compounds of known structure. For example, trifluoromethylbenzene on nitration gives only one product, which has been shown to be the 3-nitro derivative by conversion to the known 3-nitrobenzoic acid by concentrated sulfuric acid:

Orientation in Aromatic Substitution

The reaction most studied in connection with the orientation problem is nitration, but the principles established also apply for the most part to the related reactions of halogenation, sulfonation, alkylation, and acylation. Some illustrative data for the nitration of a number of mono-substituted benzene derivatives are given in below. The table includes the percentage of ortho, meta, and para isomers formed, along with their reactivities relative to benzene. We see that there is a wide range of reactivity according to the nature of the substituent, and that the ortho, meta, and para positions are *not* equally reactive. Although these substituent effects may appear complex, they are related closely to substituted alkenes.

*Orientation and Rate Data for Nitration of Some Monosubstituted Benzene Derivatives*aa



Substituent, Y	Orientation % ortho	% meta	% para	Relative reactivity
—H	—	—	—	1
—CH_3	56.5	3.5	40	24
—$C(CH_3)_3$	12.0	8.5	79.5	15.7
—CH_2Cl	32.0	15.5	52.5	0.302
—Cl	29.6	0.9	68.5	0.033
—Br	36.5	1.2	62.4	0.030
—NO_2	6.4	93.2	0.3	$\sim 10^{-7}$
—$CO_2C_2H_5$	28.3	68.4	3.3	0.003
—CF_3		100		
—$\overset{\oplus}{N}(CH_3)_3$		89	11	

[a]The data are representative but will vary to some extent with the reaction conditions and nature of the substituting agent.

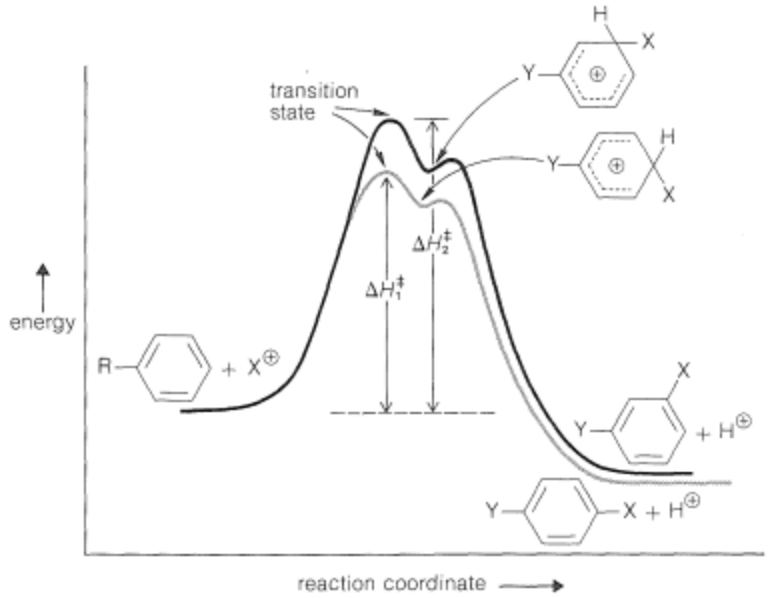
Electronic Effects

It is helpful to construct an energy diagram for substitution by an electrophilic X⊕X⊕ of a benzene derivative, C6H5YC6H5Y, in which YY is a substituent group. The rate of substitution at any one position will depend on the height of the energy barrier between the reactants and the transition state.

Effects that act to lower the heights of the barriers increase the rates of substitution. Because the transition state and the positively charged intermediate for aromatic substitution have much the same energy, any effect that stabilizes this intermediate is likely to lower the energy of the transition state and increase the rate of substitution.

Thus under conditions of *kinetic control* the preferred arene substitution product, as in alkene addition, will be that derived from the most stable of the possible intermediates.

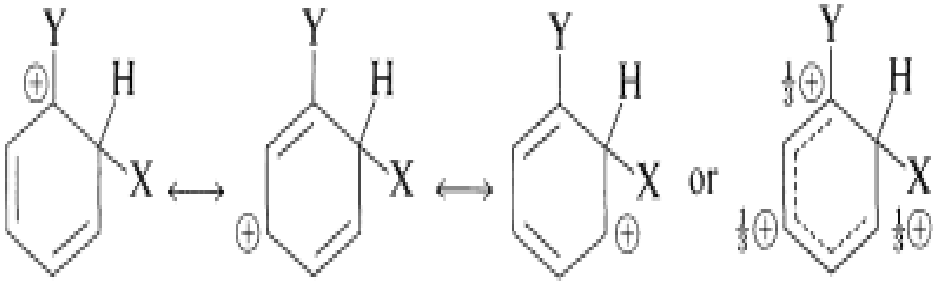
Therefore the problem of predicting relative rates and orientation in aromatic substitution becomes one of deciding what factors are likely to stabilize or destabilize the various possible intermediates relative to one another and to the ground state.



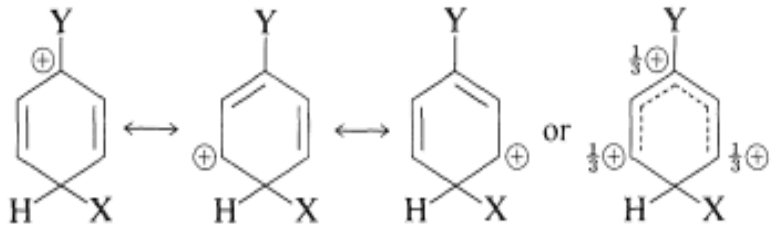
Energy diagram for the substitution of a compound C6H5YC6H5Y *in the 3 and 4 positions. It is assumed here that the relative rates are determined by differences in* ΔH‡ΔH‡ *and not in* ΔS‡ΔS‡. *Because* ΔH‡1ΔH1‡ *is less than* ΔH‡2ΔH2‡, *substitution to give the 4-isomer is "kinetically preferred".*

We now can examine the structures of the three substitution intermediates with a view to deciding how the substituent might affect their stability. According to the valence-bond method, the positive charge in the ring is dispersed mainly on alternate carbons, as shown below.

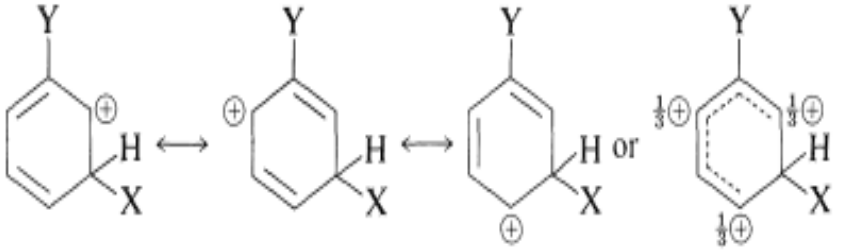
Ortho Substitution



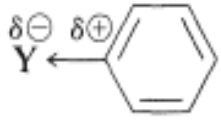
Para Substitution



Meta Substitution



The substituent YY should (and does) exert its electronic influence more strongly from the ortho and para positions than from the meta position because YY in the ortho and the para positions is close to a positively charged ring carbon. This electronic influence will be stabilizing if YY has a net electron-donating effect, and destabilizing if YY is electron withdrawing. A group can withdraw electrons relative to hydrogen if it is more electronegative than hydrogen and this is called the electron-withdrawing inductive effect. A group also can withdraw electrons by the **resonance effect**:



electron-withdrawing
inductive effect

$Y = -CF_3, -\overset{\oplus}{N}R_3$

electron-withdrawing
resonance effect

$Y = -NO_2, -CO_2R$

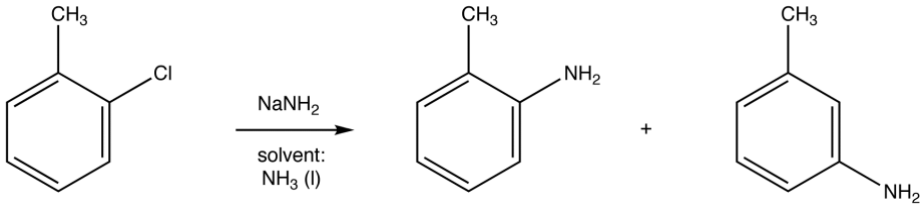
Meta-Directing Substituents

A ring substituent YY that is electron withdrawing relative to hydrogen and has no capacity to donate electrons by a resonance effect will *decrease* the reactivity of C6H5YC6H5Y, especially at the ortho and para positions. The result is a sluggish reaction (**deactivation**) with substitution occurring preferentially at the meta position. Substituents in this category are −NO2−NO2, −CF3−CF3, −CO2R−CO2R, −N⊕R3−N⊕R3, and so on (also see Tables 22-5 and 22-6). No groups are known that direct the electrophile to the meta position and, at the same time, make the phenyl derivative *more* reactive relative to benzene.

Benzyne Mechanism

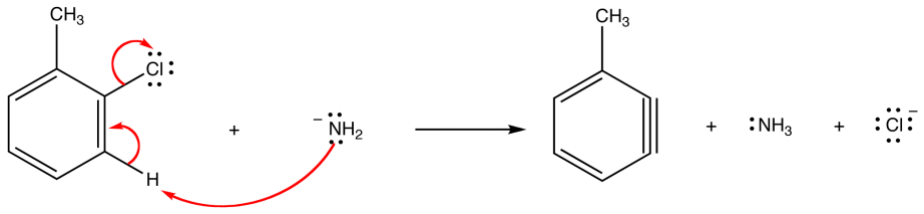
Two mechanisms have been proposed for nucleophilic aromatic substitution, one of which involves a benzyne as the intermediate and, therefore, is called benzyne mechanism.

eg:

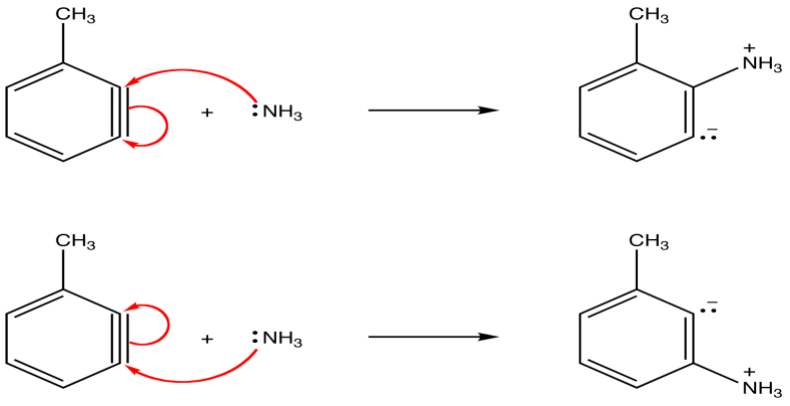


Mechanism:

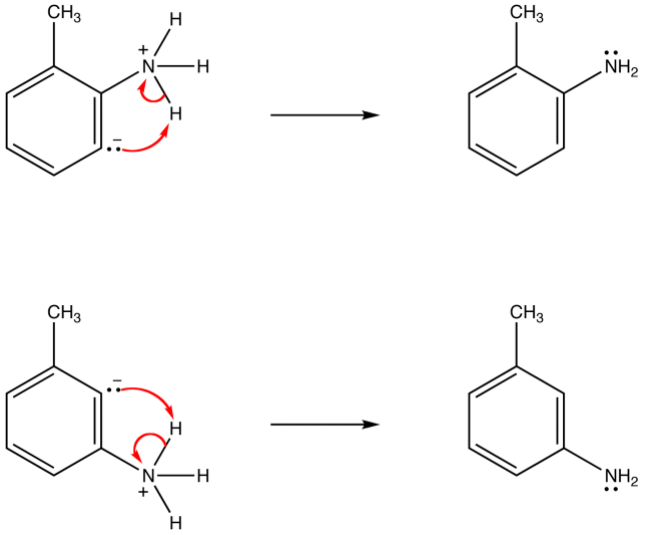
Step 1:



Step 2:



Step 3:



Step 1 requires a very strong base. Thus, for the benzyne mechanism to be operant, the medium must be very strongly basic.

UNIT – V

Aromaticity

&

Heterocyclic Compounds

2 Marks

1. What is aromaticity with example?
2. What is huckel rule?
3. Why is aromaticity important?

4. What are four conditions for aromaticity.
5. What compounds are heterocyclic?
6. Are heterocyclic compounds aromatic?
7. What are cyclic compounds used for?
8. Write the synthesis of azepine phenyl azide?
9. What is craigs rule
10. What is mean by antiromatic? Give an example.

5Marks

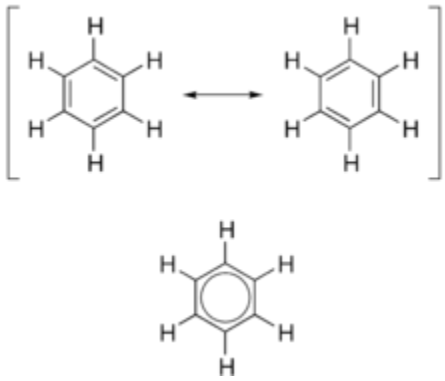
11. Explain the following rule (i) Huckels Rule (ii)craigs Rule
12. Exaplain the (18) annulenes.
13. Write the synthesis and reactions of Azoles
14. Explain the reactions of oxazole and pyrimidine?
15. Write the following synthesis of (i) Imidazole (ii) Oxazine.

10 Marks

16. Write the write a brief explanation of 5, 6 ,7 and 8 membeed rings
17. Explain the following (i) Cyclic propenium cation (ii) syndones (iii) Fullerenes
18. Write synthesis and rectionss of following heterocyclic compounds1. Pyrazole2.pyrazine3.pyridazine.

In chemistry, aromaticity is a property of cyclic(ring-shaped), planar (flat) structures with pi bonds in resonance (those containing delocalized electrons) that gives increased stability compared to other geometric or connective arrangements with the same set of atoms. Aromatic rings are very stable and do not break apart easily. Organic

compounds that are not aromatic are classified as aliphatic compounds—they might be cyclic, but only aromatic rings have enhanced stability.



Two different resonance forms of benzene (top) combine to produce an average structure (bottom)

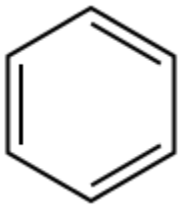
Since the most common aromatic compounds are derivatives of benzene (an aromatic hydrocarboncommon in petroleum and its distillates), the word *aromatic* occasionally refers informally to benzene derivatives, and so it was first defined. Nevertheless, many non-benzene aromatic compounds exist. In living organisms, for example, the most common aromatic rings are the double-ringed bases in RNA and DNA. An aromatic functional group or other substituent is called an aryl group.

The earliest use of the term *aromatic* was in an article by August Wilhelm Hofmann in 1855. Hofmann used the term for a class of benzene compounds, many of which have odors (aromas), unlike pure saturated hydrocarbons. Aromaticity as a chemical property bears no general relationship with the olfactory properties of such compounds (how they smell), although in 1855, before the structure of benzene or organic compounds was understood, chemists like Hofmann were beginning to understand that odiferous molecules from plants, such as terpenes, had chemical properties that we recognize today are similar to unsaturated petroleum hydrocarbons like benzene.

In terms of the electronic nature of the molecule, aromaticity describes a conjugated system often made of alternating single and double bonds in a ring. This configuration allows for the electrons in the molecule's pi system to be delocalized around the ring,

increasing the molecule's stability. The molecule cannot be represented by one structure, but rather a resonance hybrid of different structures, such as with the two resonance structures of benzene. These molecules cannot be found in either one of these representations, with the longer single bonds in one location and the shorter double bond in another. Rather, the molecule exhibits bond lengths in between those of single and double bonds. This commonly seen model of aromatic rings, namely the idea that benzene was formed from a six-membered carbon ring with alternating single and double bonds (cyclohexatriene), was developed by August Kekulé. The model for benzene consists of two resonance forms, which corresponds to the double and single bonds superimposing to produce six one-and-a-half bonds. Benzene is a more stable molecule than would be expected without accounting for charge delocalization.

In organic chemistry, Hückel's rule estimates whether a planar ring molecule will have aromatic properties. The quantum mechanicalbasis for its formulation was first worked out by physical chemist Erich Hückel in 1931. The succinct expression as the $4n + 2$ rule has been attributed to W. v. E. Doering (1951), although several authors were using this form at around the same time.



Benzene, the most widely recognized aromatic compound with six ($4n + 2$, $n = 1$) delocalized electrons.

In keeping with the Möbius-Hückel concept, a cyclic ring molecule follows Hückel's rule when the number of its π-electrons equals $4n + 2$ where n is a non-negative integer, although clearcut examples are really only established for values of $n = 0$ up to about $n = 6$.[6] Hückel's rule was originally based on calculations using the Hückel method, although it can also be justified by considering a particle in a ring system, by the LCAO method and by the Pariser–Parr–Pople method.

Aromatic compounds are more stable than theoretically predicted using hydrogenation data of simple alkenes; the additional stability is due to the delocalized cloud of electrons, called *resonance energy*.

Criteria for simple aromatics are:

The molecule must have $4n + 2$ electrons in a conjugated system of p orbitals (usually on sp^2-hybridized atoms, but sometimes sp-hybridized);

The molecule must be (close to) planar (p orbitals must be roughly parallel and able to interact, implicit in the requirement for conjugation);

The molecule must be cyclic (as opposed to linear);

The molecule must have a continuous ring of p atomic orbitals (there cannot be any sp^3atoms in the ring, nor do exocyclic p orbitals count).

Rules For Aromaticity:

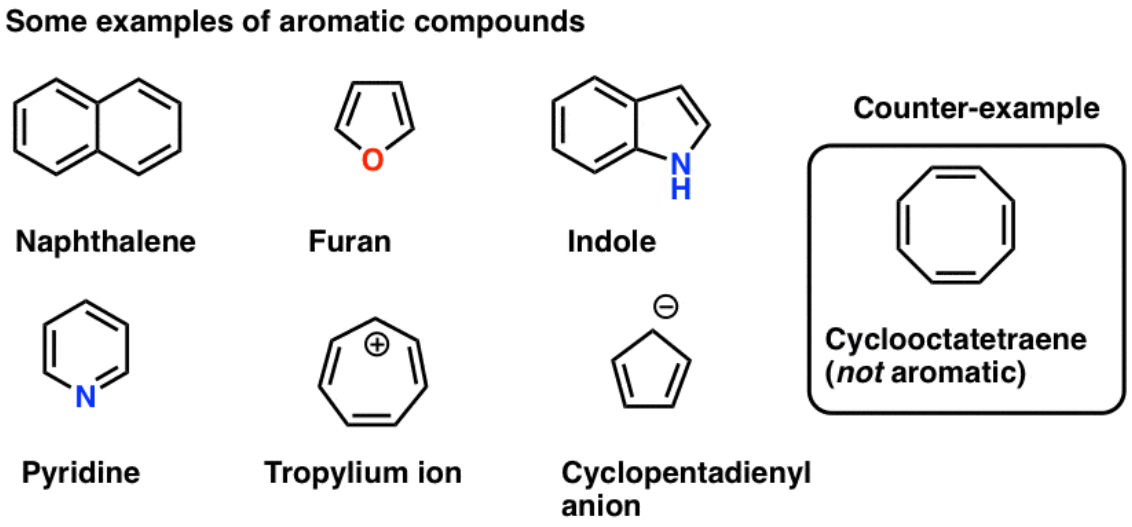
In the last post we introduced the concept of **aromaticity**, a property of some unusually stable organic molecules such as benzene. Although some aromatic molecules are indeed fragrant the term "aromaticity" actually has nothing to do with smell. We saw that aromatic molecules:

have an extremely high **resonance energy** (36 kcal/mol for benzene)

undergo **substitution** rather than **addition** reactions

have delocalized pi-electrons

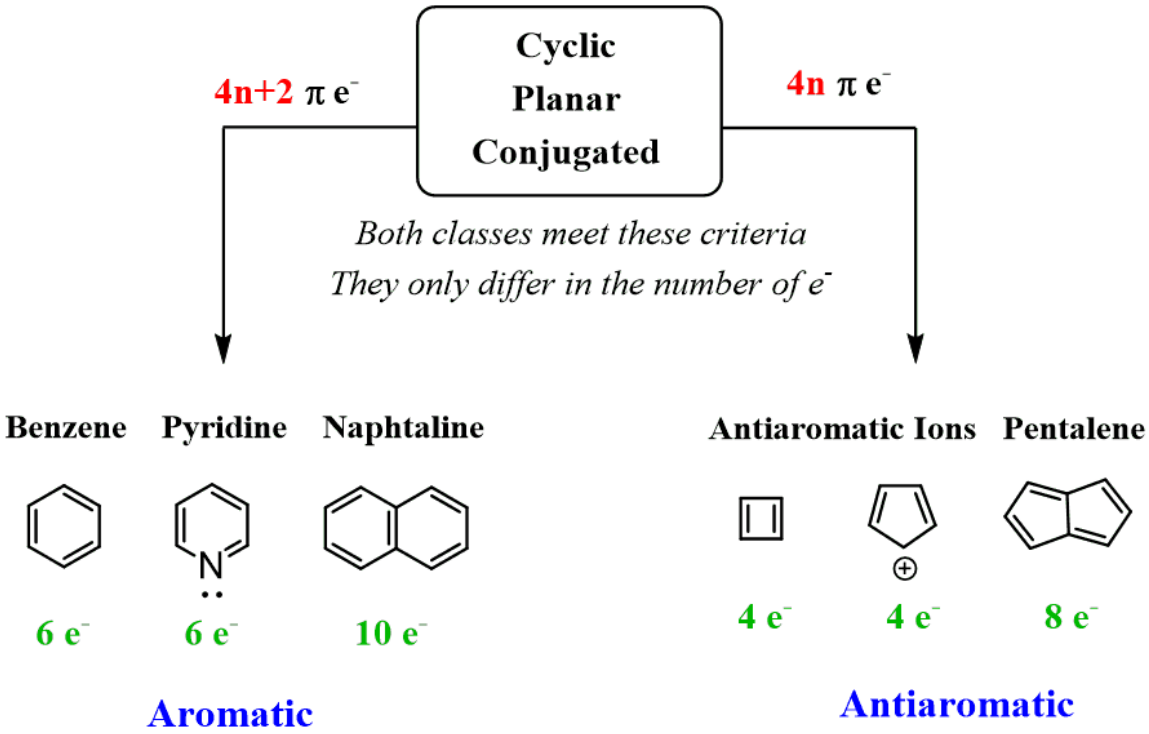
We also gave a few example of other molecules besides benzene which are aromatic, and some which look similar to benzene (e.g. cyclooctatetraene) which are not.



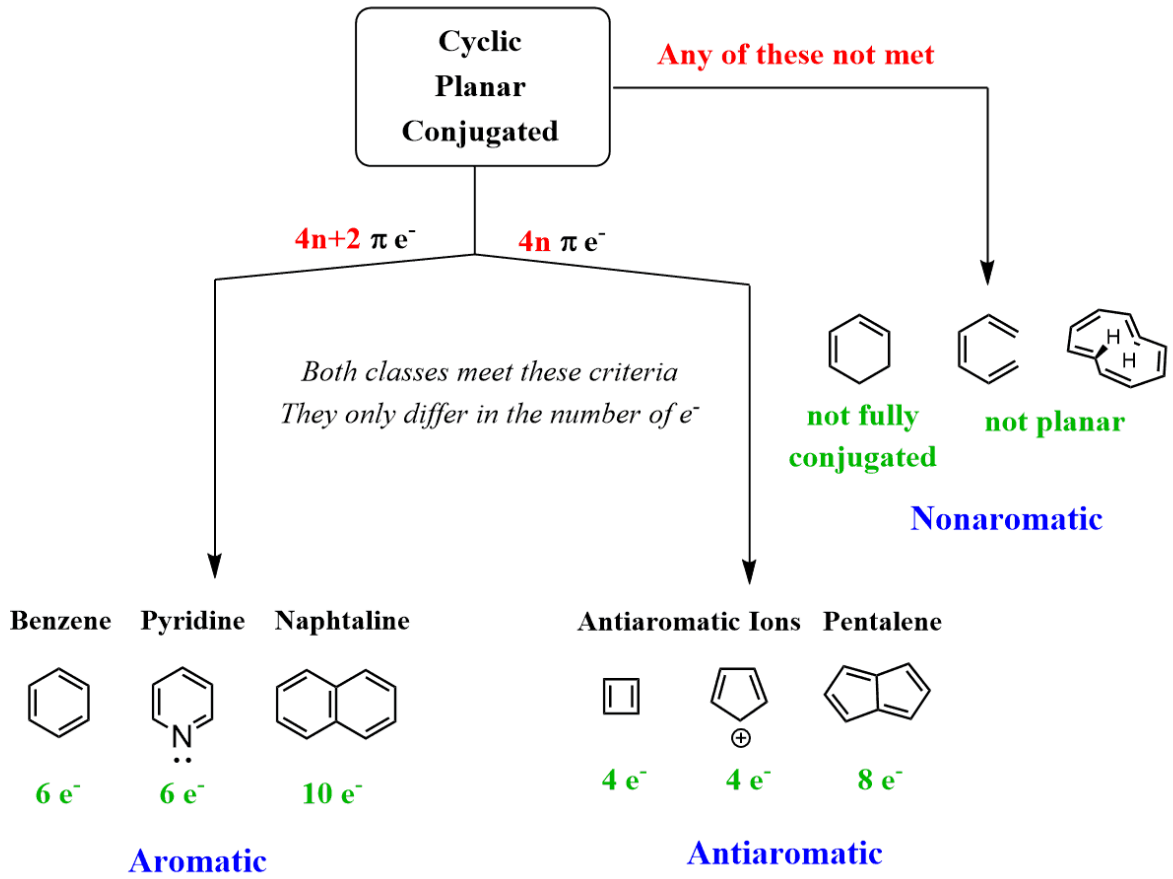
Aromatic, Antiaromatic, or Nonaromatic Compounds

We talked about aromatic and antiaromatic compounds which are recognized based on the Hückel's rule.In short, the only way aromatic and antiaromatic compounds differ is the number of electrons they have in the conjugated system. All the other criteria-being cyclic, planar and fully conjugated are a must for both categories:

Classification of Aromatic and Antiaromatic Compounds



Classification of Aromatic, Antiaromatic and Nonaromatic Compounds

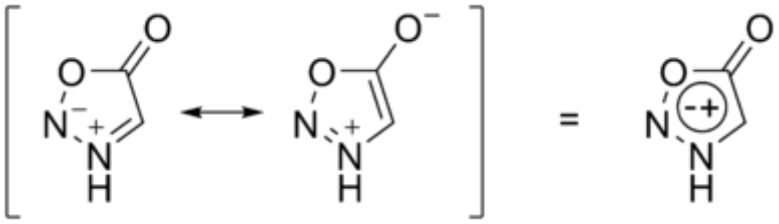


Sydnones

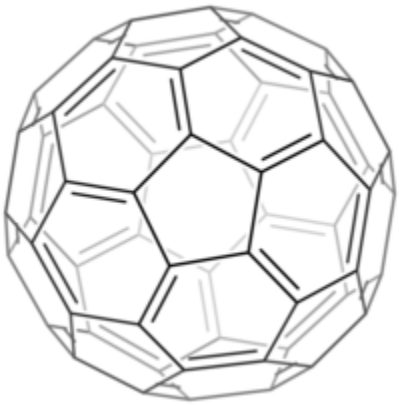
Sydnones are mesoionic heterocyclic chemical compounds possessing a 1,2,3-oxadiazole core with a keto group in the 5 position. Like other mesoionic compounds they are di-polar, possessing both positive and negative charges which are delocalized across the ring. Recent computational studies have indicated that sydnones and other similar mesoionic compounds are nonaromatic, "though well-stabilized in two separate regions by electron and charge delocalization." Sydnones are a heterocyclic compound named after the city of Sydney, Australia..

A sydnone imine in which the keto group of sydnone (=O) has been replaced with an imino(=NH) group can be found as a substructure in the stimulant drugs feprosidnine and mesocarb.

Sydnone was first prepared in 1935 by Earl & Mackney by cyclodehydration of N-Nitroso-N-phenylglycine with acetic anhydride.[5] Later work showed that this could be applied fairly generally to the nitrosamines of N-substituted amino acids.



Fullerene



Fullerene chemistry is a field of organic chemistrydevoted to the chemical properties of fullerenes. Research in this field is driven by the need to functionalize fullerenes and tune their properties. For example, fullerene is notoriously insoluble and adding a suitable group can enhance solubility. By adding a polymerizable group, a fullerene polymer can be obtained. Functionalized fullerenes are divided into two classes: exohedral fullerenes with substituents outside the cage and endohedral fullerenes with trapped molecules inside the cage.This article covers the chemistry of these so-called "buckyballs," while the chemistry of carbon nanotubes is covered in carbon nanotube chemistry.

Chemical Properties

Fullerene or C_{60} is soccer-ball-shaped or I_h with 12 pentagons and 20 hexagons. According to Euler's theorem these 12 pentagons are required for closure of the carbon network consisting of *n*hexagons and C_{60} is the first stable fullerene because it is the smallest possible to obey this rule. In this structure none of the pentagons make contact with each other. Both C_{60} and its relative C_{70} obey this so-called isolated pentagon rule (IPR). The next homologue C_{84} has 24 IPR isomers of which several are isolated and another 51,568 non-IPR isomers. Non-IPR fullerenes have thus far only been isolated as endohedral fullerenes such as $Tb_3N@C_{84}$ with two fused pentagons at the apex of an egg-shaped cage. or as fullerenes with exohedral stabilization such as $C_{50}Cl_{10}$ and reportedly $C_{60}H_8$. Fullerenes with less than 60 carbons do not obey isolated pentagon rule (IPR).

Because of the molecule's spherical shape the carbon atoms are highly pyramidalized, which has far-reaching consequences for reactivity. It is estimated that strain

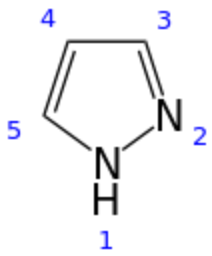
energy constitutes 80% of the heat of formation. The conjugated carbon atoms respond to deviation from planarity by orbital rehybridization of the sp^2 orbitals and π orbitals to a $sp^{2.27}$ orbital with a gain in p-character. The p lobes extend further outside the surface than they do into the interior of the sphere and this is one of the reasons a fullerene is electronegative. The other reason is that the empty low-lying π^* orbitals also have a high s character.

The double bonds in fullerene are not all the same. Two groups can be identified: 30 so-called [6,6] double bonds connect two hexagons and 60 [5,6] bonds connect a hexagon and a pentagon. Of the two the [6,6] bonds are shorter with more double-bond character and therefore a hexagon is often represented as a cyclohexatriene and a pentagon as a pentalene or [5]radialene. In other words, although the carbon atoms in fullerene are all conjugated the superstructure is not a superaromatic compound. The X-ray diffraction bond length values are 139.1 pm for the [6,6] bond and 145.5 pm for the [5,6] bond.

C_{60} fullerene has 60 π electrons but a closed shell configuration requires 72 electrons. The fullerene is able to acquire the missing electrons by reaction with potassium to form first the $K_6C^{6-}_{60}$ salt and then the $K_{12}C^{12-}_{60}$ In this compound the bond length alternation observed in the parent molecule has vanished.

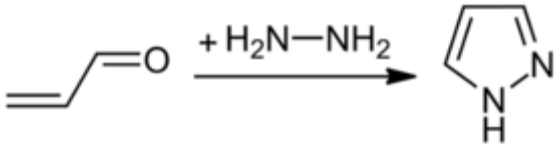
Pyrazole

Pyrazole is an organic compound with the formula$C_3H_3N_2H$. It is a heterocycle characterized by a 5-membered ring of three carbon atoms and two adjacent nitrogen atoms. Pyrazole is a weak base, with pK_b 11.5 (pK_a of the conjugated acid 2.49 at 25 °C).[2] Pyrazoles are also a class of compounds that have the ring C_3N_2 with adjacent nitrogen atoms.[3] Notable drugs containing a pyrazole ring are celecoxib (Celebrex) and the anabolic steroid stanozolol.



Preparation

Pyrazoles are synthesized by the reaction of α,β-unsaturated aldehydes with hydrazine and subsequent dehydrogenation

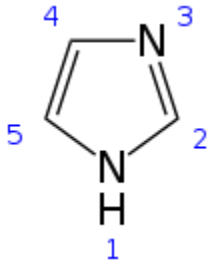


Substituted pyrazoles are prepared by condensation of 1,3-diketones with hydrazine (Knorr-type reactions). For example, acetylacetone and hydrazine gives 3,5-dimethylpyrazole

$$CH_3C(O)CH_2C(O)CH_3 + N_2H_4 \rightarrow (CH_3)_2C_3HN_2H + 2\ H_2O$$

Imidazole

Imidazole is an organic compound with the formula $C_3N_2H_4$. It is a white or colourless solid that is soluble in water, producing a mildly alkaline solution. In chemistry, it is an aromaticheterocycle, classified as a diazole, and has non-adjacent nitrogen atoms.

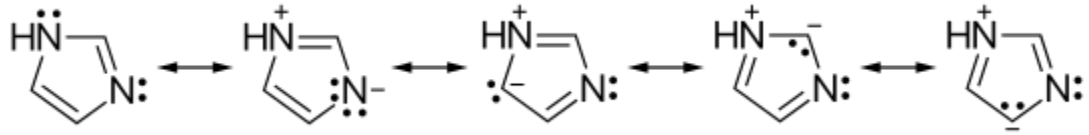


Many natural products, especially alkaloids, contain the imidazole ring. These imidazoles share the 1,3-C_3N_2 ring but feature varied substituents. This ring system is present in important biological building blocks, such as histidine and the related hormone histamine. Many drugs contain an imidazole ring, such as certain antifungal drugs, the nitroimidazole series of antibiotics, and the sedative midazolam.

When fused to a pyrimidine ring, it forms a purine, which is the most widely occurring nitrogen-containing heterocycle in nature. The name "imidazole" was coined in 1887 by the German chemist Arthur Rudolf Hantzsch (1857–1935).

Structure and Properties

Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms, because hydrogen can be bound to one or the other nitrogen atom. Imidazole is a highly polar compound, as evidenced by its electric dipole moment of 3.67 D.[11] It is highly soluble in water. The compound is classified as aromatic due to the presence of a planar ring containing 6 π-electrons(a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring). Some resonance structures of imidazole are shown below:



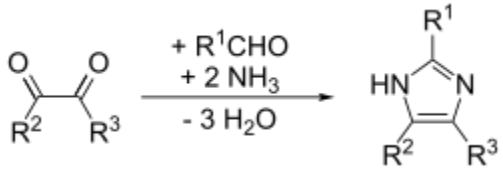
Amphoterism

Imidazole is amphoteric. That is, it can function as both an acid and as a base. As an acid, the pK_a of imidazole is 14.5, making it less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. The acidic proton is the one bound to nitrogen. Deprotonation gives the imidazolide anion, which is symmetrical. As a base, the pK_a of the conjugate acid (cited as pK_{BH^+} to avoid confusion between the two) is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is the nitrogen with the lone pair (and not bound to hydrogen). Protonation gives the imidazolium cation, which is symmetrical.

Preparation

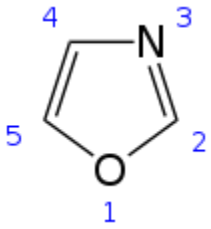
Imidazole was first reported in 1858 by the German chemist Heinrich Debus, although various imidazole derivatives had been discovered as early as the 1840s. It was shown that glyoxal, formaldehyde, and ammonia condense to form imidazole (glyoxaline, as it

was originally named). This synthesis, while producing relatively low yields, is still used for generating *C*-substituted imidazoles.

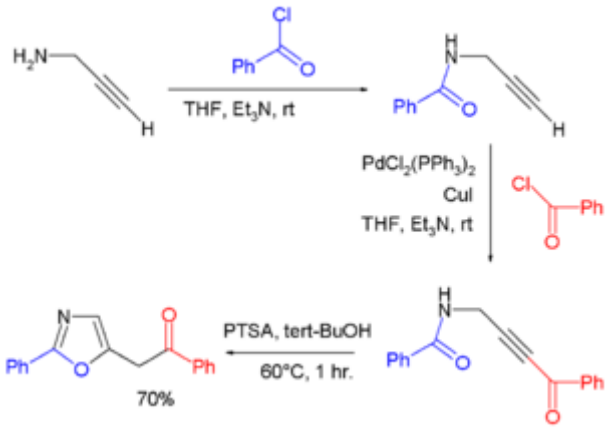


Oxazole

Oxazole is the parent compound for a vast class of heterocyclic aromatic organic compounds. These are azoles with an oxygen and a nitrogen separated by one carbon.[2] Oxazoles are aromatic compounds but less so than the thiazoles. Oxazole is a weak base; its conjugate acid has a pK_a of 0.8, compared to 7 for imidazole.

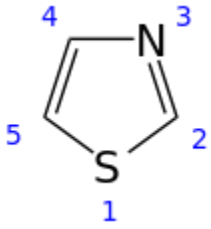


Oxazolines can also be obtained from cycloisomerization of certain propargyl amides. In one study[3] oxazoles were prepared via a one-pot synthesis consisting of the condensation of propargyl amine and benzoyl chloride to the amide, followed by a Sonogashira coupling of the terminal alkyneend with another equivalent of benzoylchloride, and concluding with *p*-toluenesulfonic acidcatalyzed cycloisomerization:



Thiazole

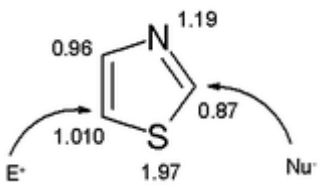
Thiazole, or 1,3-thiazole, is a heterocyclic compound that contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives. Thiazole itself is a pale yellow liquid with a pyridine-like odor and the molecular formula C_3H_3NS.[2] The thiazole ring is notable as a component of the vitamin thiamine (B_1).

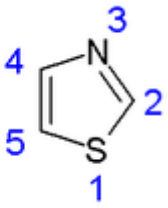


Structure

Thiazoles are members of the azoles, heterocycles that include imidazoles and oxazoles. Thiazole can also be considered a functional group. Oxazoles are related compounds, with sulfur replaced by oxygen. Thiazoles are structurally similar to imidazoles, with the thiazole sulfur replaced by nitrogen.

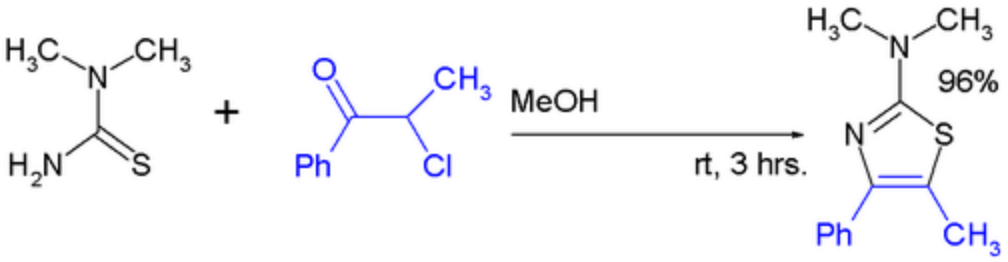
Thiazole rings are planar and aromatic. Thiazoles are characterized by larger pi-electron delocalization than the corresponding oxazolesand have therefore greater aromaticity. This aromaticity is evidenced by the chemical shift of the ring protons in proton NMR spectroscopy (between 7.27 and 8.77 ppm), clearly indicating a strong diamagnetic ring current. The calculated pi-electron density marks C5 as the primary site for electrophilic substitution, and C2 as the site for nucleophilic substitution.





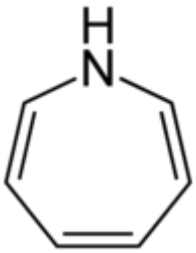
Synthesis

The Hantzsch thiazole synthesis (1889) is a reaction between haloketones and thioamides.



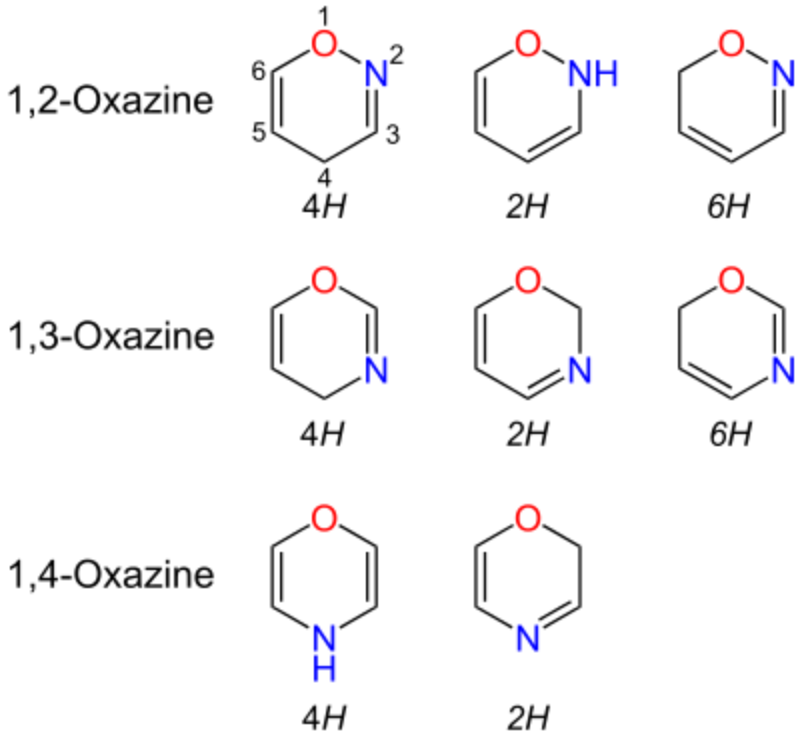
Azepines

Azepines are unsaturated heterocycles of seven atoms, with a nitrogen replacing a carbon at one position.



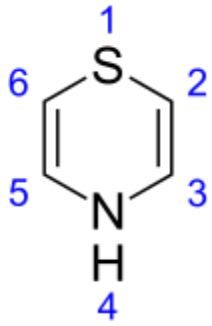
Oxazines

Oxazines are **heterocyclic compounds** containing one **oxygen** and one **nitrogen** atom in a doubly unsaturated six-membered ring. **Isomers** exist depending on the relative position of the **heteroatoms** and relative position of the **double bonds**.



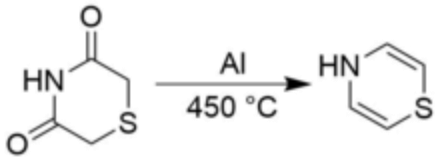
Thiazine

Thiazine is an **organic compound**containing a ring of four **carbon**, one **nitrogen** and one **sulfur** atom. There are three **isomers** of thiazine, 1,2-thiazine, 1,3-thiazine, and 1,4-thiazine, which differ by the arrangement of the nitrogen and sulfur atoms in the ring.



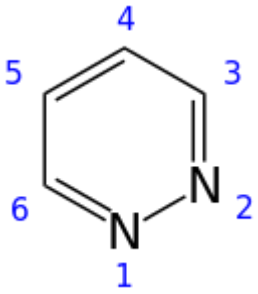
Preparation

1,4-thiazine can be prepared from the corresponding dione using **aluminium** powder at high temperature.



Pyridazine

Pyridazine is a heterocyclic organic compoundwith the molecular formula $(CH)_4N_2$. It contains a six-membered ring with two adjacent nitrogen atoms, and is aromatic.[2] It is a colorless liquid with a boiling point of 208 °C. It is isomeric with two other $(CH)_4N_2$ rings, pyrimidine and pyrazine.



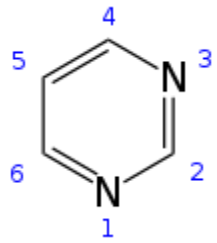
Pyridazines are rare in nature, possibly reflecting the scarcity of naturally occurring hydrazines, common building blocks for the synthesis of these heterocycles. The pyridazine structure is a popular pharmacophore which is found within a number of herbicides such as credazine, pyridafoland pyridate. It is also found within the structure of several drugs such as cefozopran, cadralazine, minaprine, pipofezine, and hydralazine.

Synthesis

In the course of his classic investigation on the Fischer indole synthesis, Emil Fischer prepared the first pyridazine via the condensation of phenylhydrazine and levulinic acid. The parent heterocycle was first prepared by oxidation of benzocinnoline to the pyridazinetetracarboxylic acid followed by decarboxylation. A better route to this otherwise esoteric compound starts with the maleic hydrazide. These heterocycles are often prepared via condensation of 1,4-diketonesor 4-ketoacids with hydrazines.

Pyrimidine

Pyrimidine is an aromatic heterocyclic organic compound similar to pyridine. One of the three diazines (six-membered heterocyclics with two nitrogen atoms in the ring), it has the nitrogen atoms at positions 1 and 3 in the ring.[250] The other diazines are pyrazine (nitrogen atoms at the 1 and 4 positions) and pyridazine (nitrogen atoms at the 1 and 2 positions). In nucleic acids, three types of nucleobases are pyrimidine derivatives: cytosine (C), thymine (T), and uracil (U).

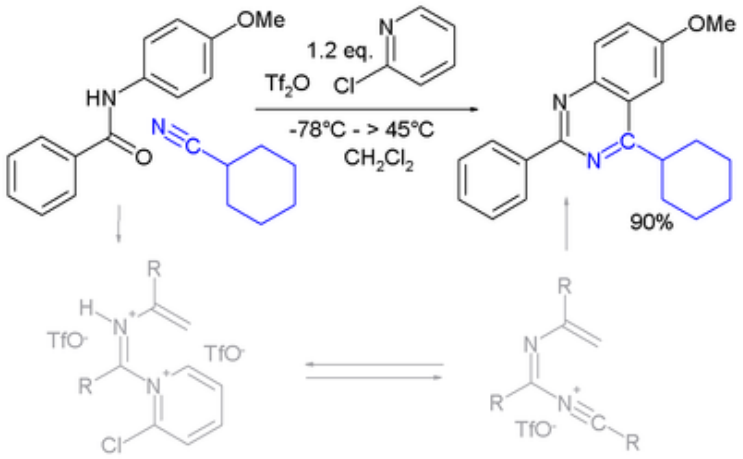


The pyrimidine ring system has wide occurrence in nature as substituted and ring fused compounds and derivatives, including the nucleotides cytosine, thymine and uracil, thiamine(vitamin B1) and alloxan. It is also found in many synthetic compounds such as barbiturates and the HIV drug, zidovudine. Although pyrimidine derivatives such as uric acid and alloxan were known in the early 19th century, a laboratory synthesis of a pyrimidine was not carried out until 1879, when Grimaux reported the preparation of barbituric acid from urea and malonic acid in the presence of phosphorus oxychloride. The systematic study of pyrimidines began in 1884 with Pinner,[8] who synthesized derivatives by condensing ethyl acetoacetate with amidines. Pinner first proposed the name "pyrimidin" in 1885. The parent compound was first prepared by Gabriel and Colman in 1900, by conversion of barbituric acid to 2,4,6-trichloropyrimidine followed by reduction using zinc dust in hot water.

Synthesis

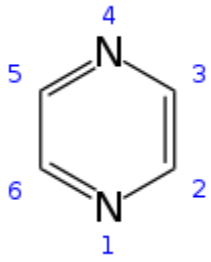
Pyrimidines can be prepared via the Biginelli reaction. Many other methods rely on condensation of carbonyls with diamines for instance the synthesis of 2-thio-6-methyluracil from thiourea and ethyl acetoacetate or the synthesis of 4-methylpyrimidine with 4,4-dimethoxy-2-butanone and formamide.

A novel method is by reaction of *N*-vinyl and *N*-aryl amides with carbonitriles under electrophilic activation of the amide with 2-chloro-pyridine and trifluoromethanesulfonic anhydride:



Pyrazine

Pyrazine is a heterocyclic aromatic organic compound with the chemical formula $C_4H_4N_2$. It is a symmetrical molecule with point group D_{2h}. Pyrazine is less basic than pyridine, pyridazineand pyrimidine.

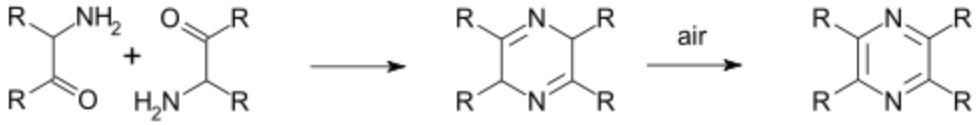


Pyrazine and a variety of alkylpyrazines are flavor and aroma compounds found in baked and roasted goods. Tetramethylpyrazine (also known as ligustrazine) is reported to scavenge superoxide anion and decrease nitric oxideproduction in human polymorphonuclear leukocytes.

Synthesis

Many methods exist for the organic synthesis of pyrazine and its derivatives. Some of these are among the oldest synthesis reactions still in use. In the Staedel–Rugheimer pyrazine synthesis(1876) 2-chloroacetophenone is reacted with ammonia to the amino ketone, then

condensed and then oxidized to a pyrazine. A variation is the Gutknecht pyrazine synthesis (1879) also based on this selfcondensation, but differing in the way the alpha-ketoamine is synthesised.



The Gastaldi synthesis (1921) is another variation