CHAPTER I
GENERAL INTRODUCTION
1.1 GENERAL HISTORY OF CHEMISTRY

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- Organic Chemistry: Functional Groups
- Raman Spectroscopy
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1.1 GENERAL HISTORY OF CHEMISTRY

Chemistry is the science of matter - a science that systematically studies the properties and composition of matter and the changes therein. Research in Chemistry is manifold. It encompasses developing an effective understanding of how substances behave, how we can protect our environs and how drugs can be developed for better living.

Chemistry has a long history of which goes back 1000,000 years. Around 5000 BC, metals came into wide use as tools and decorative items. Glass came into existence around 2000 BC. First theories of Chemistry started developing around 6th century B.C. in 3 civilizations namely Indian, Greek and Chinese. Around 1st century A.D., alchemy was established and the name Chemistry initially made its appearance. Alchemy spread rapidly from Alexandria, through Arabia and various theories were passed on to Western Europe. In the 11th, 12th and 13th century A.D. with the development of metallurgy a number of useful tools and processes were developed.

Based on his experimental work Irish born Robert Boyle propounded the law of gas behaviour with respect to temperature and pressure. An amateur chemist was first to isolate and characterize gases like nitric oxide, hydrogen chloride, ammonia and oxygen.

In the 1770’s a wealthy Frenchman Antoine Lavoisier gave a framework for understanding combustion and other chemical reactions along with composition of water which was a revolution of sorts. Dalton developed his atomic theory as well as expressed his theory in the form of symbols in his book. Gay Lussac’s law, Avogadro’s hypothesis, systemization of elements according to atomic weights by Berzelius and discovery of electricity from chemical reaction by Allessandro Volta all formed an important part of this era.

The beginning of the 19th century saw stalwarts like Sir Humphry Davy, Michael Faraday using electricity from battery to extract highly reactive metals like sodium and potassium explaining the theory of electrolysis. This period also saw the development of organic chemistry with the synthesis of urea in 1828 by Friedrich Wohler.

The concept of tetra atomicity of carbon was developed by Friedrich Kekule in 1858 and structures of organic compounds were being represented by diagrams. In
1865 the ring structure of benzene was deduced by Kekule. Van’t Hoff and Le Bel gave a three dimensional approach to the valence bonds of carbon resulting in the tetrahedron structure giving rise to the phenomenon of stereoisomerism. Bunsen and Kirchoff introduced the idea of flame photometry.

First form of Mendeleev’s periodic table took shape in 1869. As the 19th century drew to a close chemistry had greatly developed. In 1895 William Roentgen discovered X-rays which was a breakthrough. It found great application in physics and chemistry as a spectroscopic tool, in medicine as a diagnostic technique, in security systems, as a scanner at airports. In 1896 Antoine Henri Becquerel showed that Uranium was the source of radiation. Marie Curie and Pierre Curie coined the word Radioactivity and isolated new elements which were responsible for radiation. Ernest Rutherford, Paul Villard and Fredrick Soddy continued studies in area of atomic disintegration among radioactive substances which led to Rutherford to give his atomic theory in 1911. New terms like atomic number and isotopes were a result of these studies. In 1913 Niels Bohr gave the atomic model by applying the idea of quantization.

The beginning of the 20th century saw the atoms and molecules being described by a wave function which can be calculated mathematically. Combined efforts of renowned chemists like Pauli Louis de Broglie, Erwin Schrodinger and Werner Heisenberg gave the quantum theory which is the ultimate basis of our understanding of chemistry today. It explains the structure of the periodic table, bonding, reactivity, spectroscopy and so on. It unifies different branches of chemistry. 1950’s saw the advent of Computational chemistry which was developed by Clemens Roothan. In this method computers could be used to calculate the wave function and molecular properties. Development of a close relation between chemistry and physics continued through the 20th century with chemistry crossing borders and venturing into biology and material science. The 20th century also saw the addition of several new elements to the periodic table with 118 elements to date. The understanding of the Chemistry of life increased and Linus Pauling brought a revolution of sorts when he determined the fundamental structural pattern of many proteins the so called α-helix. Combined efforts of James Watson, Francis Crick, Maurice Wilkins and Rosalind Franklin saw the isolation of the ribonucleic acids (DNA and RNA) which were responsible for synthesis of various proteins needed by the cell to carry out its life functions. Science of DNA, proteins and biomolecules attracted the attention of a
large number of chemists. Various naturally occurring molecules were synthesized in
the lab among which most complex one is vitamin B12 which took nearly hundred
steps to complete. It was a landmark in the history of organic chemistry. The
discovery of Fullerene a new form of carbon containing sixty carbon atoms arranged
in a closed shell like a soccer ball created a sensation of sorts in 1985. The invention
of Scanning Tunnel Microscope was an important breakthrough in instrumentation
which helped in observing different chemical events at the molecular level during a
reaction. Intense flashes of light that are a femtosecond ($10^{-15}$ second) in duration can
be followed using this technique.

A commercial revolution of sorts has come about because of industrial
application of chemistry. Today polymers have changed the face of the modern world.
Rubbers, plastics, catalysts to speed up industrial processes, alloys with specific
properties and materials for electronic technology are being used and invented like
never before. Conducting polymers are called the future face of numerous gadgets and
smart materials. They may play an important role as conductors in the future. Though
chemistry has made our lives more comfortable the large scale manufacture of
chemicals, increase in number of industries has taken a toll on the environment.
CFC’s which were developed as a replacement for ammonia, deplete the protective
ozone layer of the earth. Though they are being phased out it is a challenge for us to
protect our environment while providing for our basic needs. The history of chemistry
is about development of chemistry from antiquity, to the modern science that it is
today. Chemistry has bridged boundaries with other disciplines and in this process it
poses challenges which we have to overcome.
1.2 TYPES OF ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS
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Synthetic methods make provision for introduction of nitro groups, the halogens, sulfonic acids, and alkyl and acyl groups.

\[
\text{E}=\text{NO}_2, \text{F}, \text{Cl}, \text{Br, I, SO}_3\text{H, SO}_2\text{Cl, R, RC}=\text{O}
\]

1) Nitration:

Nitration is the most important method for institution of nitrogen functionality on aromatic rings. Nitro compounds can be easily condensed to the corresponding amino derivatives, which can provide access to diazonium ions. There are many reagent systems that are useful for nitration. Nitration is a very common reaction and satisfactory conditions can normally be developed for both activated and deactivated aromatic compounds. Since each consecutive nitro group reduces the reactivity of the ring, it is easy to control conditions to obtain a mononitration product. If polynitration is desired, more powerful conditions are used. Concentrated nitric acid can effect nitration but it is not as receptive as a mixture of nitric acid with sulfuric acid. The agile nitrating species in both media is the nitronium ion, \(\text{NO}_2^+\), which is formed by protonation and dissociation of nitric acid. The concentration of \(\text{NO}_2^+\) is notable in more strongly acidic sulfuric acid than in nitric acid.

\[
\text{HNO}_3 + 2 \text{H}^+ \rightleftharpoons \text{H}_3\text{O}^+ + \text{NO}_2^+
\]

Following are some examples of nitration reactions. These are cases concerning mixed nitric and sulfuric acids. Reaction (1) illustrates the meta- directing effect of the protonated amino substituent. Reaction (2) is an example of dinitration.
2) Sulfonation:

The sulfonation reaction is very wide in purview and many aromatic hydrocarbons (including fused ring systems), aryl halides, ethers, carboxylic acids, amines, acylated amines, ketones, nitro compounds, and sulfonic acids have been sulfonated. Phenols can also be effectively sulfonated, but attack at oxygen may compete. Sulfonation is often carried out with sulfuric acid, but it can also be done with fuming sulfuric acid, SO₃, CISO₂OH, or other reagents.

\[
\text{ArH} + \text{H}_2\text{SO}_4 \rightarrow \text{ArSO}_2\text{OH}
\]

SO₃ reacts much more promptly than sulfuric acid – with benzene it is nearly abrupt. Sulfones are often side products. When sulfonation is accomplished on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur. An amplitude of work has been done on the mechanism by Cerfontain and coworkers. Evidences are that the electrophile varies with the reagent, though SO₃ is required in all cases, either free or combined with a carrier. In aqueous H₂SO₄ solutions the electrophile is thought to be H₂SO₄⁺ (or a combination of H₂SO₄ and H₂O⁻) at concentrations lower than 80 to 85% H₂SO₄, and H₂S₂O₇ (or a combination of H₂SO₄ and SO₃) at concentrations higher than this.

3) Halogenation:

\[
\text{ArH} + \text{Br}_2 + \text{Fe} \rightarrow \text{ArBr}
\]

a) Chlorine and Bromine: Aromatic compounds can be brominated or chlorinated by treatment with bromine or chlorine in the residence of a catalyst, most often iron. Ferric bromide or ferric chloride formed in small...
bulk from the reaction between iron and the reagent is the real catalyst. For agile substrates, including amines, phenols, naphthalene, and polyalkylbenzenes such as mesitylene and isodurene, no catalyst is needed. For amines and phenols, the reaction is so prompt that it is carried out with a dilute solution of Br₂ or Cl₂ in water at room temperature. With amines it is not feasible to stop the reaction before all the accessible ortho and para positions are substituted, because the haloamines formed in the first instance are weaker bases than the original amines and are less likely to be protonated by the liberated HX. Chlorine is more vital reagent than bromine. Phenols can be brominated solely in the ortho position by treatment at about -70°C with Br₂ in the presence of t-butyl amine or triethylenediamine, which precipitates out the liberated HBr. Primarily ortho chlorination of phenols has been attained with chlorinated cyclohexadienes, while para chlorination of phenols, phenolic ethers, and amines can be carried out with N-chloramines and with N-chlorodimethylsulfonium chloride Me₂S^+Cl^-Cl. Other chemical agents that have been used are HOCl, HOBr, N-chlorosuccinimide and N-bromosuccinimide.

For reactions in the absenteeism of a catalyst, the attacking entity is simply Br₂ or Cl₂ that has been polarized by the ring shown in (3).⁶

Affirmation for molecular chlorine or bromine as the striking species in these cases is that acids, bases, and other ions, especially chloride ion, escalate the rate about equally, though if chlorine dissociated into Cl⁻ and Cl¹, the addition of chloride should reduce the rate and the addition of acids should inflate it.

When a Lewis-acid catalyst is used with chlorine or bromine, the attacking unit may be Cl⁻ or Br⁻, formed by FeCl₃ + Br₂ → FeCl₄Br⁻ + Br⁻, or it may be Cl₂ or Br₂, polarized by the agitator. With other reagents, the striking unit in brominations may be Br⁻ or a species such as H₂OBr⁺ (the conjugate acid of HOBr), in which H₂O is a
carrier of Br⁺. With HOCl in water the electrophile may be Cl₂O, Cl₂, or H₂OCl⁻; in acetic acid it is generally AcOCl. All these types are more active than HOCl itself. When chlorination or bromination is carried out at high temperatures (e.g. 300 to 400°C), ortho –para directing groups direct meta and vice versa. A different mechanism works here, which is not completely interpreted.

b) **Iodine:** Iodine is the least receptive of the halogens in aromatic substitution. Apart from active substrates, an oxidizing agent must be available to oxidize I₂ to a better electrophile. Instances of such oxidizing agents are HNO₃, HIO₃, SO₃, peracetic acid, and H₂O₂. ICl is a superior iodinating agent than iodine itself. The actual attacking species is less clear than with bromine or chlorine. Iodine itself is too sluggish, except for active species such as phenols, where there is corroborative evidence that I₂ is the attacking species. There is proof that AcOI may be the attacking entity when peroxyacetic acid is the oxidizing agent, and I₃⁻ when SO₃ or HIO₃ is the oxidizing agent.

c) **Fluorine:** Direct fluorination of aromatic rings with F₂ is not possible at room temperature because of exceptional reactivity of F₂. It has been carried out at low temperatures (e.g., -70 to -20°C, depending on the substrate), but the reaction is not yet of preparative significance. Fluorination has also been reported with silver difluoride AgF₂, with cesium fluoroxy sulfate CsSO₄F, with acetyl hypofluorite CH₃COOF, with XeF₂, under various conditions and with various yields, in some cases by electrophilic and in other cases by free radical mechanisms. The best way of introducing fluorine into an aromatic ring still remains the Schiemann Reaction.

\[ \text{ArN}_2 + \text{BF}_4^- \xrightarrow{\Delta} \text{ArF} + \text{N}_2 + \text{BF}_3 \]

The overall effectiveness of reagents in aromatic substitution is as follows:

\[ \text{Cl}_2 > \text{BrCl} > \text{Br}_2 > \text{I}_2 \]

4) **Friedel-Crafts Alkylation**

Friedel-Crafts alkylation reactions are an important method for instituting carbon substituents on aromatic rings.
The responsive electrophiles can be either well defined carbocations or polarized complexes that contain a departing group. Various reagents can be used to produce alkylation species. Alkylation are normally associated with alkyl halides and Lewis acids or reactions of alcohols or alkenes with strong acids. Due to the participation of carbocations, Friedel-Crafts alkylations can be followed by rearrangement of the alkylation group example. Isopropyl groups are often instituted when n-propyl reactants are used\(^\text{20}\) (shown in 4).

(4)

Rearrangement can also occur after initial alkylation. Sometimes alkyl groups can also relocate from one position to another on the ring\(^\text{21}\) (shown in 5). These movements are thermodynamically controlled and carry on in the direction of reducing steric interactions between substituents.

(5)

Catalysts have been organized in the following order of overall reactivity:

\[
\text{AlBr}_3 > \text{AlCl}_3 > \text{GaCl}_3 > \text{FeCl}_3 > \text{SbCl}_3 > \text{ZrCl}_4 > \text{SnCl}_4 > \text{BCl}_3, \text{BF}_3, \text{SbCl}_5,
\]

but the reactivity order in each case depends on the substrate, reagent, and conditions.\(^\text{22}\) An important limitation of Friedel-Crafts alkylations is that with the addition of each alkyl group the reactivity of the ring for further substitution increases, which leads to polyalkylation. Polyalkylation can be reduced by using the aromatic reactant in excess.
5) Friedel-Crafts Acylation:

Friedel-Crafts Acylation is an important process for the preparation of aryl ketones. 

\[ \text{ArH} + \text{RCOCI} \xrightarrow{\text{AlCl}_3} \text{ArCOR} \]

Acylations are carried out in the presence of acyl halides and Lewis acid such as \( \text{AlCl}_3, \text{BF}_3, \) or \( \text{SbF}_5 \). Some more reagents which can be used are acid anhydrides, carboxylic acids as well as ketenes. The reactive intermediate in acylations can be a dissociated acylium ion or a complex of acyl chloride and Lewis acid. Recent studies have shown that the dominant electrophile is the protonated acylium ion when treated with benzene and its slightly deactivating derivatives (shown in 6) 

\[ \text{RCX} + \text{MX}_n \rightarrow \text{R}^-\text{C}═\text{O}^+ + (\text{MX}_{n+1})^- \]

\[ \text{R}^-\text{C}═\text{O}^+ + \text{H}^+ \rightarrow \text{R}═\text{C}═\text{O}^-\text{H} \]

(6)

Friedel-crafts acylation can be carried out with minimal amount of catalyst or sometimes with no catalyst at all. The limitations we face in alkylations like rearrangement and polyalkylation are negligible here as the RCO group serves to deactivate the ring to further attack and the reaction stops after one group is introduced.
1.3 HALOGENATIONS IN AROMATIC SYSTEMS
1.3 HALOGENATIONS IN AROMATIC SYSTEMS

1. Aqueous and Non-aqueous Medium
2. Chlorination in Aromatic Systems

1) **Aqueous and Non-aqueous Medium**

Halogenation may be defined as the process whereby one or more halogen atoms are introduced into an organic compound. The preparation of organic compounds containing fluorine, chlorine, bromine, and iodine can be accomplished by a variety of methods. The chlorine derivatives, because of the greater economy in effecting their preparation, are by far the most important of the technical halogen compounds and for this reason given primary consideration. The bromo derivatives has certain advantages because of the greater ease in effecting the replacement of this halogen in subsequent reactions or because it possesses certain pharmaceutical or dyeing properties. The fluorine derivatives are well established in the fields of refrigerants and aerosol propellants because of their stability and low boiling points.

**Chlorination:** Chlorine is reactive towards aromatic hydrocarbons, but Lewis acid catalysts are normally needed to achieve desirable rates. Rate studies show that chlorination is subject to acid catalysis, although the kinetics are frequently complex. The proton is believed to assist Cl-Cl bond breaking on a reactant-Cl$_2$ complex. Chlorination is much more rapid in polar than in nonpolar solvents. For preparative reactions, Lewis acid catalysts are used. Zinc chloride or ferric chloride can be used in chlorination. The Lewis acid facilitates cleavage of halogen-halogen bond. N-chlorosuccinimide is an alternative chlorinating agent. NCS can moderately chlorinate aromatics in nonpolar solvents by using HCl or HClO$_4$ as a catalyst. Reaction (1) and (2) show Lewis acid-catalysed.
Reaction (3) shows a high yield chlorination of acetanilide by t-butyl hypochlorite.

Reaction (4) is an acid catalysed chlorination using NCS as the reagent.

Reaction (5) describes a large scale chlorination done with NCS. The product was used for the synthesis of sulamserod, a drug candidate.

**Bromination:** Bromination exhibits similar mechanistic features to chlorination. Metallic iron which generates ferric bromide, N-bromosuccinimide (NBS) are often used in bromination. A wide variety of aromatic compounds can be brominated. Highly reactive ones, such as anilines and phenols, may undergo bromination at all activated positions. More selective reagents such as pyridinium bromide perbromide
or tetraalkylammonium tribromides can be used in such cases. Moderately reactive compounds such as anilides, halo aromatics, and hydrocarbons can be readily brominated and the usual directing effects control the regiochemistry. Use of Lewis acid catalysts permits bromination of rings with deactivating substituents, such as nitro and cyano. A solution of bromine in CCl₄ containing sulphuric acid and mercuric oxide is also a reactive brominating agent. Reaction (6) is a case of meta bromination of a deactivated aromatic. Reaction (7) is a case where all activated positions are brominated. It is interesting that the reaction occurs in acidic solution. It may be that each successive bromine addition accelerates the reaction by decreasing the basicity of the aniline and increasing the amount that is present in the neutral form.

\[ \text{Iodination: Iodinations can be carried out by mixtures of iodine and various oxidants such as periodic acid, } I₂O₅, \text{ and } NO₂. \text{ A mixture of cuprous iodide and a cupric salt can also effect iodination.} \]

Iodination of moderately reactive aromatics can be effected by mixtures of iodine and silver or mercuric salts. Hypoidoites are presumably the active iodinating species. Bis(pyridine)iodonium salts can iodinate benzene and activated derivatives in the presence of strong acids such as HBF₄ or CF₃SO₂H. Reaction (8) shows iodination using iodine monochloride done in concentrated HCl.
Fluorinations: Fluorination can be carried out using fluorine diluted with an inert gas. However, great care is necessary to avoid uncontrolled reaction. Several other reagents have been devised that are capable of aromatic fluorination. Acetyl hypofluorite can be prepared in situ from chlorine and sodium acetate. Acetyl hypofluorite shows a strong preference for o-fluorination of alkoxy and acetamido-substituted rings. N-Fluoro-bis-(trifluoromethansulfonyl)amine (N-fluorotriflimide) displays similar reactivity and can fluorinate benzene and activated aromatics.

2) Chlorination in Aromatic Systems

A number of methods are available for chlorination all of which are based on the chlorinating agents employed. Some of the important methods employed for preparing chlorine compounds are as follows:

a. Direct action of chlorine gas: Chlorine gas is greenish yellow in colour and very toxic. It is heavier than air and will sink to the ground if released from its container. It is the toxic effect of chlorine gas that makes it a good disinfectant, but it is toxic to more than just waterborne pathogens; it is also toxic to humans. It is a respiratory irritant and it can also irritate skin and mucous membranes. Exposure to high volumes of chlorine gas fumes can cause serious health problems, including death. However, it is important to realize that chlorine gas, once entering the water, changes into hypochlorous acid and hypochlorite ions, and therefore its human toxic properties are not
found in the drinking water we consume. Some reactions of chlorine gas with aromatic compounds are as follows:

\[ \text{C}_6\text{H}_6 + \text{Cl}_2 \xrightarrow{\text{FeCl}_3, \text{30-100°C}} \text{ClC}_6\text{H}_5 + \text{HCl} \]

(1)

\[ \text{C}_6\text{H}_6 + \text{Cl}_2 \xrightarrow{\text{hv, 110-120°C}} \text{CH}_2\text{C} \xrightarrow{\text{HCl}} + \text{HCl} \]

(2)

b. Sodium Hypochlorite and Calcium hypochlorite as Chlorinating Agent:
Sodium hypochlorite (NaOCl) is made up of the sodium salts of hypochlorous acid and is a chlorine-containing compound that can be used as a disinfectant. It is produced when chlorine gas is dissolved into a sodium hydroxide solution. It is liquid form, clear with a light yellow colour, and has a strong chlorine smell. Sodium hypochlorite is extremely corrosive and must be stored in a cool, dark, and dry place. Of all the different types of chlorine available for use, this is the easiest to handle.

Calcium hypochlorite Ca(OCl)$_2$ is made up of calcium salts of hypochlorous acid. It is produced by dissolving chlorine gas into a solution of calcium oxide and sodium hydroxide. Calcium hypochlorite is a white, corrosive solid that comes in tablet form or as a granular powder. It must be stored away from moisture because the tablets readily absorb moisture and generate toxic chlorine gas and a lot of heat which may be explosive. When both the reagents are treated with water they liberate hypochlorite ions which act as effective chlorinating agents. Examples of both the reagents with aromatic substrates are as follows:
c. Chlorination with Phosgene (COCl$_2$): Phosgene is a chemical compound with the formula COCl$_2$. It is a colourless gas which gained importance as a chemical weapon during World War I where it was responsible for about 85% deaths. It is a valued industrial reagent and building block in synthesis of pharmaceuticals and other organic compounds. Phosgene is used to produce acid chlorides and carbon dioxide from carboxylic acids. When treated with water it releases hydrogen chloride and carbon dioxide, where it becomes an effective chlorinating reagent. Example with aromatic compound is as follows:

\[
\text{PhCHO} + \text{COCl}_2 \rightarrow \text{PhCHCl}_3 + \text{CO}_2
\]

(5)

d. Chlorination with Sulfuryl Chloride(SO$_2$Cl$_2$)

(6)
e. Chlorination using N-chlorosuccinimide:
N-Chlorosuccinimide is used for chlorination and as a mild oxidant. It is used to generate chlorine in electrophilic substitution reactions. 42

f. Molecular Chlorine: 43 Chlorine water is prepared from bleaching powder and concentrated hydrochloric acid. It is bubbled through conductivity water to free it from HCl. It is then standardized iodometrically.
1.4 TECHNIQUES ADOPTED TO STUDY RAPID REACTIONS

- THE COMPETITION TECHNIQUE
- HYDRODYNAMIC VOLTAMMETRY
- FLOW METHODS
- RELAXATION METHOD
- FLASH PHOTOLYSIS
- MAGNETIC RESONANCE METHOD
1.4 TECHNIQUES ADOPTED TO STUDY RAPID REACTIONS

1. INTRODUCTION

Chemical reactions with half-lives as short as $10^{-7}$ seconds may be classified as fast reactions. These cannot be studied using conventional techniques that are normally used in kinetics. Recently, many electronic methods have been developed to measure times which are as short as few microseconds. There is still the problem of detecting a change in concentration in the short interval. Further, mixing together the reagents to initiate reaction is a drawback since it requires about a millisecond. For shorter times it is necessary to start with reactants which have already been mixed.

There are special techniques which are used in the study of fast reactions. These are: (i) Flow method (ii) Stopped Flow method (iii) Relaxation method (iv) Flash Photolysis (v) Quenching of fluorescence (vi) Magnetic Resonance method (vii) The Competition Technique (viii) Hydrodynamic Voltammetry

(i) FLOW METHOD

Mixtures of reactants of known initial composition are allowed to flow through a vessel of known volume at a known rate. Analysis of the mixture is made after the passage through the vessel. It is assumed that there is complete mixing of reactants just before entering the reaction vessel.

When the system operates for sufficient time, a steady state is reached i.e., there is no change in the concentration in the volume element $dV$. The steady state equation is obtained by equating the rate of entry of reactant into the volume element $dV$ to the sum of the rates of removal by flow as well as by reactions.

In 1923 Hartridge and Roughton constructed an apparatus for the study of fast reactions in solution. A schematic diagram of this apparatus is shown in Figure 1.
Figure 1.

Two solutions which are to react with each other are kept separately in two containers and sent to a mixing chamber and then to a long tub. Along the length of the tube at several points observations regarding concentration can be made. Optical methods are the most suitable for this purpose. If \( x \) is the linear velocity the time taken by an element of volume to travel a distance \( d \) is given by \( d/x \). If the measurements are made at various distances, it is possible to draw a concentration Vs time graph. The rate constant can be obtained from this curve.

The above method is suitable for measuring the rate constants of reaction whose half-life ranges from 0.001 s to about 10 s. (The measurements can also be made at a fixed distance and velocity of the flow varied. When the velocity is increased in discrete steps, the technique is referred to as the accelerated flow method.)

(ii) STOPPED FLOW METHOD

In this method the best features of static and flow methods are combined to give the best results. The apparatus used by B. Chance is shown in Figure 2.
A stopped-flow device: 40 µs dead-times

cold denatured proteins / T-jump

Figure 2.

Two reactant solutions are forced through jets into a mixing chamber. The mixing chamber is so designed to ensure mixing within a millisecond. The solution is then sent to a reaction vessel and the flow is suddenly stopped. Measurements of concentration as a function of time can be made spectrophotometrically. For a very rapid reaction the measurements should be made continuously with a high speed recorder or better with an oscilloscope whose trace can be photographed.

There are two main advantages in the stopped-flow technique. (i) There is no need to ensure a uniform flow, provided the mixing is satisfactory. (ii) The volumes of reactant solutions required are very small. Stopped-flow methods have been used for many enzyme reactions. The methods are adaptable for gas phase reactions also.

(iii) RELAXATION METHOD

Flow techniques are not useful for reactions whose half-lives are shorter than about 1ms. There are many reactions which occur with higher rates than this. For these reactions, relaxation methods are ideal. In these methods, the reaction is not started by initially mixing the reactants. Instead, the reaction is first allowed to attain equilibrium and is then disturbed in some way. The approach to a new equilibrium is studied using high speed techniques. Let us consider a simple equilibrium of the type
A + B → X

The reaction is first order in both directions. After the system comes to equilibrium, if the temperature is suddenly altered, the system would be no longer at equilibrium. If $a_0$ is the initial concentration of A and $x$ the initial concentration of X,

$$\frac{dx}{dt} = k_1 (a_0 - x) - k_{-1} x$$

At equilibrium,

$$k_1 (a_0 - x_e) = k_{-1} x_e$$

($x_e$ is the concentration of X at equilibrium). $x - x_e$ is the derivation from the equilibrium and it may be represented as $\Delta x$.

$$\frac{d}{dt} \Delta x = \frac{dx}{dt} = k_1 (a_0 - x) - k_{-1} x$$

$$= k_1 a_0 - (k_1 + k_{-1}) (x_e + \Delta x)$$

$$= -(k_1 + k_{-1}) \Delta x$$

Integration of the above equation, using the boundary condition that $\Delta x = (\Delta x)_0$ when $t=0$ gives

$$\ln \frac{(\Delta x)_0}{\Delta x} = (k_1 + k_{-1}) t$$

The quantity $1/(k_1 + k_{-1})$ is called the relaxation time, $\tau$. It is possible to determine the relaxation time experimentally. For an equilibrium, the ratio $k_1 / k_{-1}$ (equal to the equilibrium constant) is also known. Hence, the individual rate constants can be calculated.

(iv) FLASH PHOTOLYSIS

This technique for the study of a fast reaction in gas phase or liquid phase was developed by Norrish and Porter. This is an example of a pulse method. A pulse method initiates a reaction by creating new reactive species—excited electronic states, radicals, ions in the system under study.

The method uses a light flash of high intensity for a very short duration ($10^{-6}$ s) to produce atoms or free radicals or excited species in a system. These are at a fairly high concentration and undergo further reactions which are followed
spectroscopically. A schematic diagram of the flash-photolysis apparatus is given in Figure 3.

![Schematic diagram of the flash-photolysis apparatus](image)

**Figure 3.**

Since within a matter of milliseconds all the intermediates get converted into products, the opportunity must be quickly seized to study the initial excited state or those states which quickly follow from it. It is possible to synchronize a spectroscopic flash of light to follow the initial flash by some fraction of a millisecond. Thus the absorption spectra of all the species that are formed within the system can be recorded. One can not only get indications of what species are formed but also how these species give rise to others. Thus, a very direct picture of the kinetic behaviour of a fast reaction can be obtained.

The earlier techniques used photolytic flashes produced by discharging a bank of condensers through a gas. As the flash lasts for about $10^{-4}$ s, processes of shorter duration cannot be observed. Lasers are the basis of new flash techniques in the nanosecond region. The pulse from a laser has a duration of about 1 ns and so the primary absorption is complete by that time.

**(v) QUENCHING OF FLUORESCENCE**

An electronically excited molecule $A^*$ may emit radiation by fluorescence or may transfer its excess energy to another molecule. The latter takes place during a collision and is called quenching. Quenching does not require any activation energy and is generally diffusion-controlled. The two modes of energy loss from an excited molecule may be represented as follows.

$$A + h\nu \rightarrow A^*$$
The ratio of intensities of light emitted to light absorbed is referred to as fluorescent yield and is given in the present case as

\[ \frac{I_f}{I_a} = \frac{(k_f [A^\ddagger])}{(k_f [A^\ddagger] + k_q [A^\ddagger] [Q])} \]

Rearranging the above equation, we get

\[ \frac{I_a}{I_f} = 1 + \frac{k_q}{k_f} [Q] \]

The above equation is called Stern-Volmer equation. A plot of reciprocal of fluorescent yield vs the concentration of quencher is a straight line. The slope of this line gives the ratio of the rate constants, \( k_q / k_f \). The \( k_f \) can be evaluated from an analysis of absorption spectrum; therefore, \( k_q \) can also be calculated.

\textbf{(vi) MAGNETIC RESONANCE METHOD}

Using NMR and ESR spectroscopies kinetics of rapid exchange reactions can be studied. The NMR spectrum of ethyl alcohol shows the resonance of the hydroxyl hydrogen as only a single line. This is because there is no coupling between the hydroxyl hydrogen and methylene hydrogens due to rapid exchange of hydrogen atom with traces of water present. The replacing hydrogen atom need not have the same spin orientation and the methylene protons experience a coupling field which is averaged to zero. If the coupling is prevented by the removal of even traces of water, the coupling takes place and the \(-\text{OH}\) resonance has the expected multiplet structure.

It has been shown theoretically that for a coupling constant of \( J \text{ Hz} \), the coupling nucleus must exchange more rapidly than \( J/2 \) times per second for the multiplet to collapse into a singlet. The transition from coupling to non-coupling is gradual. At exchange rates slightly lower than \( J/2 \) the lines of the \(-\text{OH}\) multiplet begin to broaden; at \( J/2 \) the signal is so broad that there is no trace of line splitting. At higher rates of exchange, the broad line sharpens to a single sharp line. It is obvious that by observing the change in line shape of NMR signals the hydrogen exchange kinetics can be studied.
(vii) THE COMPETITION TECHNIQUE

The competition technique is a simple method used to study fast reactions. It is based on a competition between two reactants that do not react with one another but compete with each other to react with a reagent that is present in insufficient amount. In other words, the reaction is allowed to compete with a physical process, the rate of which is known.50

(viii) HYDRODYNAMIC VOLTAMMETRY

In this method rotating platinum electrode (RPE) versus saturated calomel electrode (SCE) is used to monitor the fall in concentration of the reagent as the reaction proceeds.51

The rotating platinum electrode is an inverted "T"-shaped glass tube 30 cm long and 5 mm in diameter, containing mercury. A platinum wire of length 1 cm and diameter 1 mm is fused at the tip of the glass tube such that 0.5 cm of it protruded out. A copper wire is dipped in the glass tube containing mercury for electrical contact. The electrode assembly is mounted on a pair of pulleys and rotated at 600 rpm by a synchronous motor. The inverted "T" shape of the glass tube, to which the platinum electrode is fused, facilitates stirring of the reaction mixture while rotating. The SCE is the positive electrode, which is the reference electrode. It is shown in Figure 4.
1.5 APPLICATION OF CHLORINATION TO DISINFECT DRINKING WATER

\[ \text{Chlorine + Organic Matter} = \text{Carcinogenic Disinfection Byproducts!} \]
1.5 APPLICATION OF CHLORINATION TO DISINFECT DRINKING WATER

Water is essential for all living organisms. It is an important ingredient of living cells nearly 60-95% by weight. A lot of water is lost by various metabolic and excretory processes. Therefore, it should be balanced by adequate intake. However, water may contain substances whether natural or anthropogenic that can affect the quality and existence of life. Pure water may be defined as water that is free of extraneous substances, whether harmless or not. But practically this is impossible to produce. On the other hand, safe water is water that is not likely to cause undesirable effects, although it may contain various contaminants. Therefore, water purification is imperative. The earliest records of water purification dates back to 2000 BCE (before the common era) in India. Various ancient writings mention various methods like exposure to sun light, filtration and heating over a fire and filtering through sand and gravel. It was only in the 8th century the use of distillation to purify water by Arabian alchemist Geber came into light. Whereas Avicenna a Persian physician recommended boiling over distillation or sedimentation as a means for travellers to purify water. In 1675, William Walcott of England was given the first patent for water purification by distillation. Various such methods continue to dominate the middle to the late 19th century which included electrolysis, voltaic action, addition of various oxidizing agents. Interestingly chlorination of water, was proposed in 1835 by Dr. R. Dunglinson. Initially large quantity was used but bad taste and odour were some problems encountered. In 1894 chlorination with bleaching powder was used to halt typhoid epidemic in Adriatic area. The beginning of the 20th century saw the setup of 1st permanent chlorination plant in Belgium in 1902. The use of chlorination rapidly increased and by 1941 over 85% of water treatment facilities used chlorination. But this process gives rise to the formation of trihalomethanes (THM) as a product and this poses potential health risk.

In a 1980 survey, over 400 separate organic chemicals were found in drinking water. The most common THM compounds found during chlorination include chloroform, bromo dichloromethane, chloro dibromomethane and bromoform. With the exception of chloro dibromomethane (placed in group C), the other THM compounds are classified by U.S. EPA as probable human carcinogens (group B2).
Other chlorinated by-products identified include various halo acids (dichloro acetic acid, trichloro acetic acid), the haloaldehydes (chlooroacetaldehyde, dichloroacetaldehyde, trichloroacetaldehyde), the haloketones (1,1,1-trichloroacetone, 1,1,3,3-tetrachloroacetone, and hexachloroacetone) the haloacetonitriles (dichloroacetonitrile, trichloroacetonitrile, trichloromethylketone, bromochloroacetonitrile, and dibromoacetonitrile), the chloropicrins (nitrotrichloromethane and trichloronitromethane), and the chlorophenols (monochlorophenols, dichlorophenols and trichlorophenols). Only a few of these chemicals have been sufficiently characterized toxicologically as to their potential human health, effects.  

Most drinking waters are prepared from natural waters which have been subjected to a series of physical and chemical processes in order to disinfect it and make it acceptable to drink. But chemical disinfectants are highly responsive by their nature and organic contaminants present in raw water may undergo alteration to form more or less toxic substances. Aqueous chlorine and monochloramine are the major disinfectants most widely used for drinking water treatment. The main objective here is to analyse the information available on the reactions of aqueous chlorine and monochloramine with various organic functional groups to predict which classes of chemical substances are most likely to undergo change under drinking water disinfection conditions. The most common reactions result in substitution (replacement of a hydrogen by chlorine), oxidation (usually meaning increased bonding of an atom to oxygen), and addition (saturation of a multiple bond). Initial reactions are often followed by others that result in carbon skeleton cleavage, decarboxylation, elimination and so on.

a. Reactive species in aqueous chlorine

When chlorine is added to water, it hydrolys:

\[
\text{Cl}_2 + \text{H}_2\text{O} \rightleftharpoons \text{HOCl} + \text{HCl} \quad (1)
\]

The product HOCl is a weak acid, however, and the definite concentration of HOCl is affected dramatically by changes in pH. HOCl has a \( pK_a \) value of 7.5

\[
\text{HOCl} \rightleftharpoons \text{OC}^- + \text{H}^+ \quad (2)
\]

32
At pH values above 7.5, the aqueous chlorine is essentially in the form of OCl⁻. At pH below 7.5, HOCl predominates. As a consequence, there are a variety of chlorinating species in chlorinated drinking water: Cl₂, HOCl, and OCl⁻. The initial amounts of each depend on the initial concentration of chlorine and pH. The approximate concentrations of the various active chlorine species at pH 7.5 are given in Table 1.

Table 1 Concentration of Active Chlorine Species in Typical Chlorinated Drinking Water

<table>
<thead>
<tr>
<th>Species</th>
<th>Concentration /M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl₂</td>
<td>1.27 x 10⁻³⁷</td>
</tr>
<tr>
<td>HOCl</td>
<td>5.00 x 10⁻⁶</td>
</tr>
<tr>
<td>OCl⁻</td>
<td>5.00 x 10⁻⁶</td>
</tr>
</tbody>
</table>

Molecular chlorine is generally more reactive than HOCl.

b. Reactive species in Aqueous Chloramine:

The situation with aqueous chloramine is even more complex. Potential equilibria in these solutions are as:

\[
\begin{align*}
\text{NH}_2\text{Cl} + \text{H}_2\text{O} & \rightleftharpoons \text{HOCl} + \text{NH}_3 & (3) \\
\text{NH}_2\text{Cl} + \text{H}^+ & \rightleftharpoons \text{NH}_3\text{Cl}^+ & (4) \\
2\text{NH}_2\text{Cl} + \text{H}^+ & \rightleftharpoons \text{NHCl}_2 + \text{NH}_4^+ & (5) \\
\text{NHCl}_2 + \text{HOCl} & \rightleftharpoons \text{NCl}_3 + \text{H}_2\text{O} & (6) \\
\text{HOCl} & \rightleftharpoons \text{H}^+ + \text{OCl}^- & (7)
\end{align*}
\]

All these chlorine containing molecules (NH₂Cl, NH₃Cl⁺, NHCl₂, NCl₃, HOCl, and OCl⁻) have been shown to be reactive species. The comparable amounts of each of these in a particular solution depend on the concentrations and the pH. If drinking water contains low initial concentration of both Free available chlorine (FAC) and
NH₃ (about $10^{-5}$ M), NCl₃ predominates at very low pH, at which most of the NH₃ is tied up as NH₄⁺, but the amount of NCl₃ drops rapidly as the pH increases. The concentration of NCl₂ is low at low pH, rises to a maximum at pH 5, where it accounts for most of the active chlorine, and diminishes again at higher pH. The concentration of the inorganic chlorammonium ion (NH₃Cl⁻) is very low at neutral pH, but it is also a more potent chlorinating agent than NH₃Cl. As expected, HOCl is important at only low pH and OCl⁻ at high pH. Table 2 gives typical concentrations for the various species in chloramine treated drinking water at pH 7.5.

**Table-2: Concentrations of Ammonia and Active Chlorine Species in NH₃ and Cl₂ Treated Drinking Water**

<table>
<thead>
<tr>
<th>Species</th>
<th>Concentration /M</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH₃Cl</td>
<td>$0.80 \times 10^{-6}$</td>
</tr>
<tr>
<td>NHCl₂</td>
<td>$4.53 \times 10^{-6}$</td>
</tr>
<tr>
<td>NCl₁</td>
<td>$6.14 \times 10^{-8}$</td>
</tr>
<tr>
<td>HOCl</td>
<td>$9.21 \times 10^{-11}$</td>
</tr>
<tr>
<td>OCl⁻</td>
<td>$9.21 \times 10^{-11}$</td>
</tr>
<tr>
<td>NH₃</td>
<td>$5.96 \times 10^{-8}$</td>
</tr>
<tr>
<td>NH₄⁺</td>
<td>$4.53 \times 10^{-6}$</td>
</tr>
<tr>
<td>NH₃Cl⁺</td>
<td>$2.5 \times 10^{-13}$</td>
</tr>
</tbody>
</table>

Reaction of organic compound with chlorinated or chloraminated water can result in substitution, addition, oxidation and so on. Despite this diversity of reaction results, the initiating step in most of the reactions has a common mechanistic characteristic. It is a nucleophilic substitution by an electron rich group (the nucleophile) on a halogen.

\[
\text{Nu}^- + \text{Cl} - \text{X} \rightarrow \text{Nu} - \text{Cl} + \text{X}^-
\]  

\[
\text{H} - \text{Nu}^- + \text{Cl} - \text{X} \rightarrow \text{:N} - \text{Cl} + \text{H}^+ + \text{X}^-
\]

34
These reactions are characterized by the transfer of an electrophilic (electron deficient) chlorine from Cl- X to the nucleophile and are often acid or base catalysed. In essence, a Cl' is exchanged. Reaction (9) can also be described as an electrophilic substitution or chlorination. Both reactions are usually oxidations in the theoretical sense, since they most often result in an increase in the oxidation state of the atom or group Nu. Cl – X may be Cl – Cl, Cl – OH, Cl – O', Cl – NH₂, Cl – NHCl or Cl – NCl₂. The reactivity of the different electrophilic of chlorine donors that have been mentioned varies greatly. A general order of reactivity may be constructed as follows:

Cl₂ > HOCl, OCl’, NCl₃ > NH₂Cl > NHCl₂

When such Cl’ donor react with a nucleophile, a substitution or association product is formed. For example,

\[
\text{Me}_2\text{N}^- + \text{HOCl} \rightarrow \text{Me}_2\text{N} - \text{Cl} + \text{H} - \text{OH} \quad (10)
\]

\[
\text{H} - \text{C}_6\text{H}_4 - \text{OH} + \text{HO} - \text{Cl} \rightarrow o - \text{and} \ p - \text{Cl} - \text{C}_6\text{H}_4 - \text{OH} + \text{H} - \text{OH} \quad (11)
\]

\[
\text{Ph}_2\text{S}^- + \text{Cl} - \text{Cl} \rightarrow \text{Ph}_2\text{S}^- - \text{Cl} + \text{Cl}' \quad (12)
\]

In some cases, the initial product is not stable and undergoes further reaction. For example, the electrophilic chlorine may simply be transferred to another nucleophile. Alternatively the products of chlorination may undergo rearrangement or may suffer elimination, and carbon – carbon bond cleavage may occur. An example of this is haloform reaction in which chloroform is generated by the chlorination of methylketone in drinking water:

\[
\text{C}_{10}\text{H}_7\text{COCH}_3 + 3\text{HOCl} \rightarrow 3\text{HOCl} + \text{C}_{10}\text{H}_7\text{COOCCl}_3
\]

\[
\text{C}_{10}\text{H}_7\text{COOH} + \text{CHCl}_3
\]

(13)

This type of change involves highly chlorinated intermediates. Finally, Cl' donors may react with carbon – carbon multiple bonds, since the π electrons serve as electron – rich centre to combine with Cl'. In general, “ionic” reactions are favoured for the reactive species found in aqueous chlorine and chloramine. The reactivity of homocyclic aromatic compound varies widely and depends on the types of substituents attached to the ring. Simple alkyl group substituted aromatic compounds
like toluene and xylene do not react to any significant extent in chlorinated drinking water. On the other hand, aromatics substituted with more strongly electron-donating groups, such as the methoxy group (example anisole), are quite reactive, as are phenolic compounds. In aromatic compound having activating (electron-donating) groups, the reaction rate increases with the number of groups attached to the ring. In contrast to this most aromatic compounds are not expected to undergo significant transformation in chloraminated water. The presence of chlorinated phenol is often associated with undesirable taste and odour in chlorine-treated water. The reactivity of phenol is quite different from that of other aromatic because they can ionize at higher pH values. Lee and Soper and Smith studied the rate of reaction of phenol with aqueous chlorine at pH values from 5 to 12 and found that the reaction mechanism involves chlorination of phenoxide by HOCl. The observed rates of chlorination vary for example, p-chlorophenol is four times less reactive than phenol, but the maximum observed rate constant for the reaction of o-chlorophenol is approximately equal to that of phenol.

Ring substitution in some phenols may involve replacement of other functional groups on the ring. Chlorination of phenolic acids, such as 4-hydroxybenzoic acid results in replacement of the carboxyl group by a chlorine atom. The reactions of aqueous chlorine with polyhydroxylated aromatics can yield numerous products. 1,3-dihydroxilated aromatics are believed to be one of the main sources of chloroform produced on chlorination of humic substances in drinking water. Other aromatic compounds that have been shown to react with aqueous chlorine include 4-nitrophenol and 3-hydroxybenzoic acid and a series of polynuclear aromatics. Both chlorinated and oxidation products were observed for the latter. In contrast Burleson et al. found no ring substitution products from phenylalanine upon super chlorination of waste water, only the expected products from chlorination of the terminal amino group.
1.6 DRUGS PREPARED FROM CHLORO MOIETIES OF AROMATIC SUBSTRATES
1.6 DRUGS PREPARED FROM CHLORO MOIETIES OF AROMATIC SUBSTRATES

A drug is a compound that combines with a living organism, activating a physiological effect. They have been used by human beings since time immemorial to get rid of the pain and illness. Fighting disease with drugs is a timeless struggle. The earliest reference about medicine preparations in writing came from India in the Rigveda and from China in their Material Medica 2500-3000 B.C. All the drugs used were of vegetable origin as various herbs, roots, berries and barks were employed. The era of synthetic drugs had to wait till the technique of synthetic organic chemistry became well advanced and physiology of human organism became well known. The beginning of synthetic medicinal chemistry was mostly made in Germany.

Introduction of halogen atom in aromatic substrates results in entities which are more lipophilic and so less water soluble. Therefore, halogen atoms can be used to improve the penetration of lipid membranes. Aromatic halogen groups are far less reactive than aliphatic halogen groups, which can exhibit considerable chemical reactivity. The most popular halogen substituents are the less reactive aromatic fluorine and chlorine groups. The replacement of a hydrogen atom in an active molecule by a halogen can deeply modify the potency, duration, even the nature of the pharmacological effect.

Among the halogens chlorine and its compounds like hypochlorous acid have long been known for their germicidal properties. Bleaching powder (CaOCl₂) has been used extensively for many years as a disinfectant, as it is very cheap. By the addition of boric acid to bleaching powder, a mixture may be obtained which contains free hypochlorous acid and calcium diborate, and very well adapted as a dressing for wounds and the treatment of septic conditions.

Another form of hypochlorite solution known as Dakin’s solution prepared by the action of a solution of sodium carbonate and sodium bicarbonate on bleaching powder containing 0.45 % to 0.5 % sodium hypochlorite. Dakin’s solution has largely been used for treatment of wounds. Later Dakin introduced organic
chloramines as a substitute for sodium hypochlorite. Chloramines were prepared by the action of hypochlorite solution on organic compounds containing the imino -(NH) or amino (-NH₂-) groups. As a result chloramines containing the (-NCl-) group, and dichloramines containing the (-NCl₂-) are produced. The best known and most used of the Chloramines is the substance under the name of Chloramine T. It has been used for the treatment of infected wounds especially in military surgery. It is used as a disinfectant lotion in cases of infectious diseases, such as scarlet fever, measles.
1. CHLOROQUINE

Chloroquine is 4-aminoquinoline. This drug is used in the treatment and prevention of malaria.

Historical background: Chloroquine was discovered in 1934 by Hans Andersag and coworkers at the Bayer laboratories who named it “Resochin”. Its use was avoided for many years being too toxic for human use. After US sponsored clinical trials it was introduced into clinical practice in 1947 for the prophylactic treatment of malaria.

Medicinal use: Chloroquine phosphate may be substituted or added in the treatment of amoebic liver abscess. It is also used in some autoimmune disorders like rheumatoid arthritis and lupus erythematosus. It is also used in clinical trials as an investigational anti retro viral in humans with HIV-I / AIDS and as a potential antiviral agent against chikungunya fever. The radio sensitizing and chemosensitizing properties of chloroquine are being exploited in anticancer strategies in humans.

Chloroquine has a very high volume of distribution as it diffuses into the body’s adipose tissue. It has been associated with cases of retinal toxicity if provided at higher doses for longer times. This may lead to blurred vision and blindness. Chloroquine also behaves as a lysosomotropic agent as it accumulates in the lysosomes of cells in the body. This character accounts for its antimalarial activity. The drug concentrates in the acidic food vacuole of the parasite and interferes with essential processes. Its lysosomotropic properties further allow for its use for in vitro experiments pertaining to intracellular lipid related diseases, autophagy, and apoptosis.
Diclofenac is 2-(2.6-dichloranilin) phenyl acetic acid. This drug is used as an anti-inflammatory and analgesic. It can be taken or applied to reduce inflammation and helps in relieving pain in certain conditions.

**Historical Background:** Diclofenac was first synthesized by Alfred Sallmann and Rudolf Pfister and introduced as Voltaren by Ciba-Geigy (now Novartis) in 1973.

**Medicinal use:** Diclofenac is used to treat inflammatory disorders like arthritis, rheumatoid arthritis, polymyositis, dermatomyositis, spondylarthritis, gout attacks and pain management in cases of kidney stones and gall stones. It is also used in the treatment of acute migraines. It is effective against menstrual pain and endometriosis. In many countries, eye drops are sold to treat acute and chronic non-bacterial inflammation of the anterior part of the eyes.

Diclofenac can be combined with opioids if required. Under trade names such as Combaren and Voltaren Plus, a fixed combination of diclofenac and codeine (50 mg each) is available in Europe. It has also been found effective against all strains of multidrug resistant E. coli with a MIC of 25 micrograms /ml. Thus, it can treat mild urinary tract infections caused by E. coli. and is under investigation for the treatment of tuberculosis.
Chloramphenicol is 2,2-dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl) propan-2-yl] acetamide. This drug is used as an antibiotic. Chloramphenicol is useful for treatment of a number of bacterial infections like meningitis, plague, cholera, and typhoid fever. It is available intravenously, by mouth, and as an eye ointment.

**Historical background:** Chloramphenicol was discovered in 1947. It was originally derived from the bacterium Streptomyces venezuelae, by David Gottlieb, and introduced into clinical practice in 1949, under the trade name Chloromycetin. It was the first antibiotic to be manufactured synthetically on a large scale.

**Medicinal use:** The original use of chloramphenicol was in the treatment of typhoid. It may be used as a second-line agent in the treatment of tetracycline-resistant cholera. Because of its excellent blood brain barrier penetration chloramphenicol remains the first choice treatment for Staphylococcal brain abscesses. Chloramphenicol is active against three main bacterial causes of meningitis: Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae. In the West, chloramphenicol remains the drug of choice in the treatment of meningitis patients with severe penicillin allergy. Recent research suggests that chloramphenicol could also be applied to frogs to prevent their widespread destruction from fungal infections. It is also a life-saving cure for chytridiomycosis which is a fungal disease in amphibians.

Chloramphenicol is extremely lipid-soluble; it remains relatively unbound to protein and is a small molecule. It has a large volume of distribution and penetrates effectively into all tissues of the body, including the brain. Distribution is not uniform, with highest concentrations found in the liver and kidney, with lowest in the brain and cerebrospinal fluid. Chloramphenicol increases the absorption of iron. It is still widely used in topical preparations (ointments and eye drops) for the treatment of bacterial conjunctivitis. The risk of aplastic anaemia on using chloramphenicol is estimated to be less than one in 224,716 prescriptions.
4. CHLOR TETRACYCLINE

Chlortetracycline (trade name Aureomycin, Lederle) is a tetracycline antibiotic, the first tetracycline to be identified. Chlortetracycline, a member of tetracycline family, is a broad spectrum antibiotic that is commonly given to poultry, swine and livestock. In veterinary medicine, chlortetracycline is commonly used to treat conjunctivitis in cats.¹⁰¹

**Historical background:** Chlortetracycline was discovered in 1945 by Duggar Working at Lederle Laboratories under the supervision of Yellapragada Subbarow. Duggar identified the antibiotic as a product of an actinomycetes he cultured from a soil sample collected from Sanborn Field at the University of Missouri.¹⁰² The organism was named Streptomyces aureofaciens and the isolated drug, Aureomycin because of their golden colour.

**Medicinal use:** Chlortetracycline can be used to prevent, control and treat health problems as well as enhance growth rates in chickens, turkeys, ducks, swine, calves, beef cattle, and other animals.¹⁰³ It has been in clinical use since 1948.¹⁰⁴ Chlortetracycline enters the environment primarily through the application of animal manure to fields.¹⁰⁵ Chlortetracycline appears to be reunited in the top soil layers after land application.¹⁰⁶ Chlortetracycline has been shown to be relatively persistent in soil.¹⁰⁵ The stability of chlortetracycline in water depends on pH, temperature, light, and other parameters.¹⁰⁷
5. MEPACRINE

Mepacrine is a drug with several medical applications. It is mainly used as an antiprotozoal, antirheumatic and an intrapleural sclerosing agent.\(^{108}\)

**Historical background:** Mepacrine was initially approved in the 1930’s as an antimalarial drug. It was extensively used during the second world war by US forces fighting in the Far East to prevent malaria.\(^{109}\) Scientists at Bayer in Germany first synthesized mepacrine in 1931. The product was one of the first synthetic substitutes for quinine although later superseded by chloroquine.

**Medicinal use:** As an antiprotozoal it is used to target giardiasis. Giardiasis that is very resistant may even require a combination of mepacrine and metronidazole.\(^{108}\) Mepacrine is also used for the treatment of systemic lupus erythematosus, indicated in the treatment of discoid and subcutaneous lupus erythematosus, particularly in patients unable to take chloroquine derivatives.\(^{110,108}\)

As an intrapleural sclerosing agent, it is used as pneumothorax prophylaxis in patients at high risk of recurrence, eg. Cystic fibrosis patients.\(^{108}\) In addition to medical applications, mepacrine is an effective in vitro research tool for the epifluorescent visualization of cells, especially platelets. Mepacrine is a green fluorescent dye taken up by most cells. Platelets store mepacrine in dense granules.\(^{111}\) The use of mepacrine for non-surgical sterilization for women has also been studied.\(^{112}\)

\[
\begin{align*}
\text{CH}_3 & \quad \text{NH} - \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{CH}_3 \\
\text{Cl} & \quad \text{O} - \text{CH}_3
\end{align*}
\]

**Mepacrine**
1.7 REFERENCES
1.7 REFERENCES

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