CHAPTER - 1

INTRODUCTION
"Every great advance in science has issued from
a new audacity of experimentation”.

1.0 IMPORTANCE OF NEW SYNTHETIC METHODS:

The science of organic synthesis has grown very rapidly in size over past
century to the point where only serious participants can hope to make major
contribution. In intellectual depth and intrinsic complexity, there are not many
other areas of science, as chemistry; which is formidable and demanding.

This is an exciting time in synthetic chemistry. Keeping up with new
developments in synthetic chemistry is a difficult task. The pace at which new
reactions, reagents and catalyst are being discovered and successfully implemented
is nothing short of breathtaking. Thus, organic chemists are constantly on the
alert for faster, simpler and cheaper preparative methods.

Catalyst played a major role in establishing the economic strength of the
chemical industry in the first half of the 20th century.1 Catalysis, with it’s great
established place in chemistry, on the rise of 21st century will play a leading
role in this revolution. The growing awareness of unacceptability of many
conventional reagents and catalysts and resulting legislation will give a major
impetus to the search for “efficient technology,” including new synthetic methods.2
Numerous reagents are available for various useful synthetic transformations in
organic synthesis. These are widely classified as organic reagents and inorganic
reagents.

The careful choice of a reagents is frequently critical if satisfactory results
in synthetic application are to be achieved. Organic reagents are well established
reagents in chemistry. The benefits of inorganic reagents in organic synthesis
are also nevertheless.

The successful application of a new or relatively poorly understood inorganic
reagent as a catalyst in organic synthesis can be understood by knowing several
types of inorganic reagents applicable in various methods of organic synthesis.
There are several types of inorganic reagents.

1.1 INORGANIC SOLID SUPPORTED REAGENTS IN ORGANIC
SYNTHESIS.

The use of an organic supported reagents in organic synthesis is an important
and challenging topic to explore an efficient and mild methods of preparations.
Traditional methods of preparing supported catalyst have involved two stages:
(i) Rendering a metal compound into a finely divided form on a support and
(ii) The conversion of the metal compound to a metallic or metal oxide state. For the supported reagent (ii) is not applicable, so that the preparation is reduced to the first dispersion stage which is achieved by impregnation, adsorption from solution, coprecipitation or deposition. The second stage where applicable, involves calcination or reduction - that is, thermal treatment in an inert atmosphere or in oxygen or hydrogen. Some common inorganic support materials are listed below.

Table 1.1: Some common inorganic support materials.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Support</th>
<th>Typical surface area/ m$^2$g$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Silica gel</td>
<td>300 - 600</td>
</tr>
<tr>
<td>2.</td>
<td>Alumina</td>
<td>100 - 300</td>
</tr>
<tr>
<td>3.</td>
<td>Montmorillonites</td>
<td>050 - 300</td>
</tr>
<tr>
<td>4.</td>
<td>Pillared montmorillonite</td>
<td>200 - 500</td>
</tr>
<tr>
<td>5.</td>
<td>Zeolites</td>
<td>300 - 600</td>
</tr>
<tr>
<td>6.</td>
<td>Charcoals, generally wood charcoals</td>
<td>300 - 1000</td>
</tr>
<tr>
<td>7.</td>
<td>Inorganic (mineral) fluorides, (CaF$_2$)</td>
<td>5 - 20</td>
</tr>
</tbody>
</table>

More systematic investigation of the solid surfaces has lead to the new established fields of polymer supported reagent chemistry and the importance of zeolite materials in their own right, even outside of petroleum chemistry can justify independent reviewing. The main emphasis here will be on the supported reagents obtained by the deliberate introduction of reagent into or into an inert, generally porous, inorganic support in liquid phase organic reactions. There are numerous potential advantages but the most important are,-

1. Good dispersion of active (reagent) sites can lead to significant improvements in reactivity.
2. The constraints of the (molecular dimensions) pores and the characteristics of the surface adsorption can lead to useful improvements in reaction selectivity.
3. Solids are generally easier and safer to handle than liquid or gaseous reagent.
4. The supported reagent is easy to remove from the final reaction mixture (filtration), hence minimizing cross contamination between inorganic and organic components.
5. Some supported reagents may easily reused.
The major disadvantages are, -

1. The cost of adding an extra components (the support) into the reaction.
2. The difficulty in ensuring good mixing of solid-liquid or solid-liquid-gas (e.g. in liquid phase oxidations using air) mixtures.
3. The trapping of organic molecules in the supported reagent pores.

1.1.1 Types of supported inorganic reagents:

Supported reagents based on inorganic materials have been known for almost 30 years and the development of the subject is apparent from the study increase in the number of research articles. The original principle behind the use of supported reagents was to achieve an increase in the effective surface area and hence activity of potentially useful but insoluble inorganic reagent via their dispersion over high surface area inert support materials. Based on their activity there are various types of inorganic supported reagents.

1.1.1.1 Clay minerals:

Clay minerals are solids with a lamellar structure. The reactants can diffuse into the regions between the layers and react there. Clays consist of a combination of a tetrahedral and octahedral layers. Continuous sheets of silica tetrahedra are linked via three corners and edge-sharing octahedra (Al$^{3+}$ or Mg$^{2+}$), respectively.

[i] Natural Clays: There exists a wide variety of natural clays with different combinations of tetrahedral and octahedral layer.

[ii] Kaolinites clay: Important for preparative purpose are kaolinites with a T-O-T-O-T-O sequence of layers (1:1 type) and vermiculites with T-O-T-O-T-T-O-T sequence of layers (1:2 type). Partial exchange of the metal atom with other metal is frequent and leads to defective sites of higher activity.

[iii] Pillared clays: Pillared clays are produced by insertion of large cationic species between the layers, leading to a basal spacing of up to 20 Å. The powders that are actually employed for synthetic purpose are agglomerates of small clay crystallites with a mesopore texture.

(a) Layered Silicates
(b) Pillared Clay
Clays were the first acid catalysts used on a very large scale in the petroleum industry for cracking and isomerisation reaction. For synthetic purpose, clays have considerable potential as environmental friendly acidic catalysts with large accessible surface area. Clays have recently been used for synthesis of tetrapyrroles.7

According to Balogh and Laszlo,8 the following features of clays are important for their application as catalysts and supports:

1. The layered structure into which molecules of the right size and affinity can diffuse and react. Incarporation of organic molecules leads to swelling of the clay and the spacing of the layers can increase from 12-14 Å to 17-20 Å.

2. The high ionic strength, due to the charged layers that can stabilize charge separation in transition states.

3. The possibility of highly dehydrated clays to produce radicals.

4. In the montmorillonite clay various spacing of layer observed is as follows.

Table 1.2: Spacing of layers in montmorillonite clay.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Montmorillonite</th>
<th>Basal spacing (Å)</th>
<th>Interlayer spacing (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dehydrated</td>
<td>9 - 10</td>
<td>2 - 3</td>
</tr>
<tr>
<td>2.</td>
<td>Organic pillar</td>
<td>13 - 16</td>
<td>6 - 9</td>
</tr>
<tr>
<td>3.</td>
<td>Inorganic pillar</td>
<td>20 - 25</td>
<td>13 - 18</td>
</tr>
</tbody>
</table>

A problem for the organic chemist is the bewildering variety of natural clays that are used and investigated by the specialists. For example glossary of Balogh lists clays with more than 50 different names. However, only few types are used frequently and are commercially available.
Table 1.3: Commercially available clays.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of reagents</th>
<th>Surface area (m²/g)</th>
<th>Supplier</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Bentonite</td>
<td>Not given</td>
<td>Aldrich</td>
<td>9(i)</td>
</tr>
<tr>
<td>2.</td>
<td>Bentonite</td>
<td>Not given</td>
<td>Fluka</td>
<td>9(ii)</td>
</tr>
<tr>
<td>3.</td>
<td>Montmorillonite K-10</td>
<td>220 - 270</td>
<td>Aldrich, Fluka</td>
<td>9</td>
</tr>
<tr>
<td>4.</td>
<td>Montmorillonite KSF</td>
<td>10 - 30</td>
<td>Aldrich, Fluka</td>
<td>9</td>
</tr>
</tbody>
</table>

1.1.1.2 Application of inorganic reagents based on clays:

In recent years a number of reagents based on acid, activated clays were developed (from overview Carnelis).\textsuperscript{10} Especially montmorillonites, ion-exchanged with FeCl₃, ZnCl₂ (clayzic) and similar Lewis acid, were studied as catalysts for a variety of acid catalysed reactions. Metal nitrate supported on clay K-10 such as Cu(NO₃)₂ (claycop), Fe(NO₃)₃ (clayfen) or Ti(NO₃)₃ are also clay-based reagents. These are used as stoichiometric nitrating or oxidizing reagents suitable for the preparation on a small scale. Some of the applications of clays in various types of reaction are summarised in the following Table.(1.4)

Table 1.4: Application of clay in organic synthesis.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Oxidative deprotection of silyl ether</td>
<td>11</td>
</tr>
<tr>
<td>2.</td>
<td>Coupling of thiols to disulfides</td>
<td>12</td>
</tr>
<tr>
<td>3.</td>
<td>Conversion of toluene to methylphenyl - methane</td>
<td>13</td>
</tr>
<tr>
<td>4.</td>
<td>Diels - Alder reaction using K-10-Fe(III)</td>
<td>14</td>
</tr>
<tr>
<td>5.</td>
<td>Protection of carbonyl as a thioacetal</td>
<td>15</td>
</tr>
<tr>
<td>6.</td>
<td>Acylation of aromatic using carboxylic acids</td>
<td>16</td>
</tr>
<tr>
<td>7.</td>
<td>Cyclodehydration of α-ω-dicarboxylic acid</td>
<td>17</td>
</tr>
<tr>
<td>8.</td>
<td>Formation of pyrroles and pyrazoles by solid acid catalyzed ring closures.</td>
<td>18</td>
</tr>
<tr>
<td>9.</td>
<td>Acetyl formation of aldehydes using K-10 clay</td>
<td>19</td>
</tr>
<tr>
<td>10.</td>
<td>Regeneration of aldehydes from bisulfites using KSF-clay.</td>
<td>20</td>
</tr>
<tr>
<td>11.</td>
<td>Synthesis of isocyanates from carbamates using K-10.</td>
<td>21</td>
</tr>
</tbody>
</table>
1.1.1.2 Zeolites in organic synthesis:

Zeolites, also called molecular sieves, are the most prominent class of microporous solids. Zeolites are aluminosilicates and have a three-dimensional crystalline pore or channel structure into which molecules of appropriate size can diffuse and react. The dimensional framework is built up of silica and alumina tetrahedra arranged into several types of secondary building blocks. Each time a Si$^{4+}$ is replaced by an Al$^{3+}$, an additional cation has to be present in order to neutralize the charge. Usually the sodium form is synthesized. By ion-exchange procedure, other cations can be introduced. Exchange of Na$^+$ by H$^+$ gives strongly acidic materials. The ratio of Si/Al determines the polarity, the acidity and the exchange capacity of the zeolites, parameters that also control the catalytic properties of these materials. Zeolites with high Si/Al ratio (>10) are strongly acidic, acid stable, have a low exchange capacity and are hydrophobic. Zeolites with a lower Si/Al ratio show medium acidity, are rather stable towards bases, have a high exchange capacity and are hydrophilic. Zeolites are important catalysts for photochemistry.

1.1.1.2.1 Selectivity in organic synthesis:

The capability of molecular sieves to organize and to discriminate molecules with high precision is responsible for their shape selective properties.

(i) Reactant selectivity: Only molecules that are able to enter the zeolite channels react.

(ii) Product selectivity: Only molecules that are able to leave the zeolite channels are found in the product mixture.

(iii) Restricted transition state selectivity: Reaction occurs only when the required transition state can be formed in the zeolite cavities.

Some of the more interesting ways that zeolite and other molecular sieves have been modified to enable the change in catalytic properties are listed below:

1. Increase in Si/Al ratio to encourage "super acidity" and enabling the catalysis of hydrocarbon reaction such as alkane-cracking and menthol transformations.
2. Increasing Bronsted acidity to increase C-alkylation at the expense of O-alkylation in phenols.
3. Changing from Bronsted to Lewis acid centres to change the course of reaction from an acid catalyzed hydrolysis to an acid catalysed rearrangement.
4. Incorporation of C-18 chain to enable a zeolite to operate as a solid interface catalyst between water and water immiscible ester layer.

5. Bifunctional (acid-base) character of zeolite to enable simultaneous acid activation of epoxy compounds and base activation of an attacking nucleophile (overall ring opening reaction)

6. Asymmetric synthesis zeolites.

7. Partial oxidation of organic using titanium silicates (Notable TS-1) and other molecular sieves.

| Table 1.5: Chemical composition and properties of zeotype molecular sieves. |
|--------------------------------|-------------------------|-------------------------|
| Type                      | Chemical composition   | Properties              |
| Zeolite                  | (Si\(^{4+}\)-O-Al\(^{3+}\)-Si\(^{4+}\))  
H\(^{+}\) Or M\(^{+}\)   | Negatively charged framework  
hydrophilic with ion exchange and acid sites |
| Silicalites              | Si-O-Si-O-Si            | Neutral frameworks hydrophobic  
without ion exchange and acid sites |
| AIPO\(_{4}\)             | Al\(^{3+}\)-O-P\(^{5+}\)-O-Al\(^{3+}\)  | Neutral frameworks hydrophobic  
without ion exchange and acid sites |
| SAPO                     | Si\(^{4+}\)-O-Al\(^{3+}\)-O-P\(^{5+}\)  
H\(^{+}\) or M\(^{+}\)   | Neutral frameworks hydrophobic  
without ion exchange and acid sites |

Chemische Fabrik Uetikon\(^{25}\) offers also a variety of zeolites.

ZSM-5 is most popular zeolite in organic synthesis. ZSM designates many of mobil’s silicate and aluminosilicate materials and stands for “Zeolites Socony Mobil.” Zeolite ZSM-5 can be constructed from five member ring building units. These units link together to form chains and the interconnection of these chains leads to the formation of the channel system in structure. The combination of these building units results in a framework containing two intersecting channel systems, one sinusoidal and the other straight. The pore openings are elliptical 10-member rings. There are 12 unique T atom sites in ZSM-5.
Fig 1.2 Structure of ZSM-5

Table 1.6: Application of some zeolite in organic transformations:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cyclodehydration of 2-benzoylbenzoate acid.</td>
<td>26</td>
</tr>
<tr>
<td>2.</td>
<td>Oxidative photodecarboxylation reaction of N-protected amino acid with FSM 16</td>
<td>27</td>
</tr>
<tr>
<td>3.</td>
<td>TBHP, Cr or V Molecular sieves catalysed oxidation of primary alkyl amines and anilines to corresponding nitro compound.</td>
<td>28</td>
</tr>
<tr>
<td>4.</td>
<td>N-acylation of carboxylic acid using zeolites HY</td>
<td>29</td>
</tr>
<tr>
<td>5.</td>
<td>Michael addition of simple ethoxytrimethyl silanes using 4 A° molecular sieves</td>
<td>30</td>
</tr>
<tr>
<td>6.</td>
<td>Transesterification using zeolite Hβ</td>
<td>31</td>
</tr>
</tbody>
</table>
1.1.3 Al-Oxides (Aluminas) and Si-Oxide (Silicas) supported reagents:

Silicas and aluminas are the most important oxidic materials, but titania, ziraconia, magnesia and other oxides are use quite frequently.32

Particle size, surface area, pore structure and acidity are the parameters that determine the properties of these oxides as catalyst or as supports. To be useful, these supports must have a large surface area, for aluminas usually 120-300 m²/g and for silica 50-400 m²/g.

Alumina33 is a term used for various hydrated and anhydrous aluminium oxides that exist in many different polymorphic form. The most important form is called γ-Al₂O₃ and is formed around 450° C, which has high surface area. Alumina based supported reagents solid bases have been used in a wide variety of organic reactions including Michael-addition, enolizations, condensations, elimination and oxidation. Alumina itself possesses moderately basic surface sites but its basicity can be significantly increased by adsorption of fluoride, alkoxides, hydroxides and even AlPO₄.

Many common reducing agents such as LiAlH₄, NaBH₄, Bu₃SnH, pyridine-BH₃, Metallic K or Na₂S were immobilized on silica or alumina.34,35 On the oxidic supports, many oxidants also immobilized: Cr-oxides, KMnO₄, NaIO₄, Cerium salts and SeO₂ etc. Some of the reagents which can be used safely in organic synthesis are as follows.

Reagents supported on silica and alumina are of interest for the synthetic chemist because silica gel and aluminium oxide are available in every organic laboratory. Silicas and aluminas have basic as well as acidic centers.

Metal cations such as Na⁺ can be produced on silica surface by saturating the gel with aqueous solutions of metal compounds such as hydroxides, acetates and carbonates.

Table 1.7: Use of silica supported reagents in various organic transformations.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Silica supported imine used for Knoevenagel Condensation</td>
<td>36</td>
</tr>
<tr>
<td>2.</td>
<td>Aldehydes to nitriles using SiO₂-NaHSO₄</td>
<td>37</td>
</tr>
<tr>
<td>3.</td>
<td>SiO₂-Morpholine used for Henry reaction</td>
<td>38</td>
</tr>
<tr>
<td>4.</td>
<td>FeCl₃-Silica used for coupling of dimethoxy aromatics</td>
<td>39</td>
</tr>
<tr>
<td>5.</td>
<td>Silica / t-BuOOH in oxidation of sulfide to sulfoxide</td>
<td>40</td>
</tr>
<tr>
<td>6.</td>
<td>NaOH-SiO₂ catalyzed Aldol reaction</td>
<td>41</td>
</tr>
<tr>
<td>7.</td>
<td>Silica / H₂SO₄-NaNO₂ in N-nitrosation of secondary amines</td>
<td>42</td>
</tr>
</tbody>
</table>
Table 1.8: Application of alumina supported reagents in organic synthesis.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Michael addition.</td>
<td>43</td>
</tr>
<tr>
<td>2.</td>
<td>Knoevengeel reaction.</td>
<td>44</td>
</tr>
<tr>
<td>3.</td>
<td>Aldol reactions and other condensations.</td>
<td>45</td>
</tr>
<tr>
<td>4.</td>
<td>Nitrile hydration.</td>
<td>46</td>
</tr>
<tr>
<td>5.</td>
<td>Sonogashira coupling and cyclization reaction.</td>
<td>47</td>
</tr>
<tr>
<td>6.</td>
<td>Mannich reaction of terminal alkynes.</td>
<td>48</td>
</tr>
</tbody>
</table>

1.1.4 Carbon supported reagents in organic synthesis:

Two types of carbons are important materials for preparative chemistry.

(i) Active carbon (charcoal): In synthetic chemistry, these materials are used for removing colored or highly polar impurities, and as a support for metallic catalysts. Due to Bansel et al\textsuperscript{49} characterize the structure of active carbons as "stacks of flat aromatic sheets cross linked in a random manner" and "quite different from graphite." The physico-chemical properties of the carbon surface such as adsorption potential, redox and acidic behavior are due to functional groups such as carboxylic acids, phenols, lactones, aldehydes, ketones, quinones or hydroquinones (fig 1.3). Active carbons are generally used as powder with particle diameters of 1-100 \textmu m and have BET surface areas of 800-1500 \text{m}^2/\text{g} in a complex network of pores.

(ii) Graphite: It is highly ordered layered material where the layers consist of Sp\textsuperscript{2} hybridized carbon atoms arranged in a hexagonal structure (extended benzene). The layers are held together by Vander Wall's forces at a distance of 3.4 \text{Å}. This distance increases when guest molecules diffuse into the interlayer space. Graphite is used for intercalating reagents and sometimes as a support for metal catalyst.\textsuperscript{50}

![The layered structure of graphite.](image-url)
Fig. 1.4 Schematic presentation of different functional groups found on the surface of activated carbons.

Table 1.9: Use of carbon supported reagents in organic synthesis.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>C-alkylation carbonyl-ene-reaction.</td>
<td>51</td>
</tr>
<tr>
<td>2.</td>
<td>Synthesis of Pyran using ZnCl graphite.</td>
<td>52</td>
</tr>
<tr>
<td>3.</td>
<td>Rearrangement of O-aryl-N,N-dimethyl-thiocarbamates</td>
<td>53</td>
</tr>
<tr>
<td>4.</td>
<td>Benzylic C-H Barylation of alkylbenzene.</td>
<td>54</td>
</tr>
<tr>
<td>5.</td>
<td>Chemoselective hydrogenolysis of idoarenes.</td>
<td>55</td>
</tr>
<tr>
<td>6.</td>
<td>Reformatzky reaction</td>
<td>56</td>
</tr>
</tbody>
</table>

1.2 POLYMER SUPPORTED REAGENTS IN ORGANIC SYNTHESIS.

1.2.1 Introduction: 57, 58

Polymer based reagents have been shown to be very versatile. Functionalized polymers are used both as reagents and as catalysts. The discovery of polymers and their use in organic synthesis was made by Merrifield in 1963, for his method of solid phase peptide synthesis. These are closest to soluble organic molecules, both with respect to structure as well as reactivity. Indeed there is a gradual change from solution to solid state behaviour when going from soluble to swellable to highly cross-linked polymers. Almost every chemical function (acid, base, ion pair, oxidant etc.) that is used in solution chemistry can be attached to a polymer.
There are some advantages claimed for polymer supported reagents and catalysts.

1. Easier separation and work-up.
2. Better regeneration and recycling properties.
3. New (or better) selectivities and faster reactions (or lower reaction temperature).
4. Solid reagents are safer, less toxic, more stable and easier to handle.
5. Less effluent and waste problems.
6. Possibility to work in the continuous reaction mode.

There are some limitations for the use of such reagents, which are as follows.

1. Wide number of reagents or catalyst is not commercially available or it’s preparation is ill described.
2. Higher costs.
3. Product(s) absorbs strongly.
4. Accessibility of the active surface sites etc.

Some of the above problems can be solved by proper choice of the solvent or a slight change of the support, good stirring and the use of materials with adequate pore size are important in preparative organic chemistry. The applications of polymer supported reagents have been summarized. (Table 1.10), (Table 1.11).
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Functional Polymer</th>
<th>Application as reagents</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>$\mathbf{P}-(\text{Ph}-2)$</td>
<td>Witting reaction.</td>
<td>59</td>
</tr>
<tr>
<td>2.</td>
<td>$\mathbf{P}-(\text{CH}_2\text{N}^+\text{Me}_3)$ $\text{BH}_4^-$</td>
<td>Reductions of carbonyl compound to alcohol.</td>
<td>60</td>
</tr>
<tr>
<td>3.</td>
<td>$\mathbf{P}-(\text{CH}_2\text{N}^+\text{Me}_3)$ $\text{IO}_4^-$</td>
<td>Oxidation of phenols and sulfides.</td>
<td>61</td>
</tr>
<tr>
<td>4.</td>
<td>$-(\text{CH}_2)_6\text{N}=\text{C}=\text{N}_n$</td>
<td>Peptide synthesis</td>
<td>62</td>
</tr>
<tr>
<td>5.</td>
<td>$\mathbf{P}-(\text{CH}_2\text{N}=\text{C}=\text{NR})$&lt;br&gt;a. $R=\text{Pr}$; b. $R=\text{Et}$</td>
<td>Conversion of acids to Peptide synthesis</td>
<td>63</td>
</tr>
<tr>
<td>6.</td>
<td>$\mathbf{P}-(\text{C}=\text{C}=\text{NEt}_2)$</td>
<td>Conversion of acid to mixed anhydrides, esters and amides</td>
<td>64</td>
</tr>
<tr>
<td>7.</td>
<td>$\mathbf{P}-(\text{SO}_2\text{Cl})$</td>
<td>Oligonucleotide synthesis</td>
<td>65</td>
</tr>
<tr>
<td>8.</td>
<td>$\mathbf{P}-(\text{COCl})$</td>
<td>Conversion of acid to acid chloride.</td>
<td>66</td>
</tr>
<tr>
<td>9.</td>
<td>$\mathbf{P}-(\text{N}=\text{Br}_2)$</td>
<td>Oligonucleotide synthesis</td>
<td>67</td>
</tr>
<tr>
<td>10.</td>
<td>$\mathbf{P}-(\text{S}-\text{CH}_2\text{Li}^+)$</td>
<td>Homologation of alkyl iodides and diiodides.</td>
<td>68</td>
</tr>
<tr>
<td>11.</td>
<td>$\mathbf{P}-(\text{CH}_2\text{Cl})$</td>
<td>Monoprotection of dithiols.</td>
<td>69</td>
</tr>
<tr>
<td>12.</td>
<td>$\mathbf{P}-(\text{CH}_2\text{Cl})$</td>
<td>Monoprotection of diphenols and diols.</td>
<td>70</td>
</tr>
<tr>
<td>13.</td>
<td>$\mathbf{P}-(\text{CH}_2\text{Cl})$</td>
<td>Glycoside synthesis</td>
<td>71</td>
</tr>
<tr>
<td>14.</td>
<td>$\mathbf{P}-(\text{COOCOR})$</td>
<td>Conversion of amines to amides, alcohol to ester</td>
<td>72</td>
</tr>
<tr>
<td>15.</td>
<td>$\mathbf{P}-(\text{OH})$</td>
<td>Synthesis of 1, 2, 3, 4-tetrahydro-β-carbolines.</td>
<td>73</td>
</tr>
<tr>
<td>16.</td>
<td>$\mathbf{P}-(\text{N})$</td>
<td>Acid acceptor. Polymeric Girard reagent.</td>
<td>74</td>
</tr>
</tbody>
</table>
Table 1.11: Polymeric catalyst & its use in organic synthesis.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Functional Polymer</th>
<th>Application as catalyst</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>P–COPh</td>
<td>Photosensitizer</td>
<td>75</td>
</tr>
<tr>
<td>2.</td>
<td>P–N–C0—(Cj—OH–CH2CH2COO&lt;</td>
<td>Acylation</td>
<td>76</td>
</tr>
<tr>
<td>3.</td>
<td>P–CO–OH</td>
<td>UV absorbers</td>
<td>77</td>
</tr>
<tr>
<td>4.</td>
<td>P–C12H25COO–</td>
<td>Hydrolysis of Schiff bases.</td>
<td>78</td>
</tr>
<tr>
<td>5.</td>
<td>P–N–X</td>
<td>Hydrolysis of phenyl esters. Hydrolysis of p-nitrophenyl acetate.</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>X = H</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>X = CONH2 + CONPh(OH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>P–CH2OCO–COPh</td>
<td>Cycloaddition and dimerization of olefins</td>
<td>80</td>
</tr>
<tr>
<td>7.</td>
<td>P–SO3H</td>
<td>Cyclization, condensation, rearrangement, hydration, alkylation.</td>
<td>81, 82</td>
</tr>
<tr>
<td>8.</td>
<td>P–COOH</td>
<td>Hydrolysis, esterification</td>
<td>83</td>
</tr>
<tr>
<td>9.</td>
<td>P–AlCl3</td>
<td>Acetal formation, estrification</td>
<td>84</td>
</tr>
<tr>
<td>10.</td>
<td>P–SO3HBF3</td>
<td>Alkylation of olefins</td>
<td>85</td>
</tr>
</tbody>
</table>
Introduction

1.3 PHASE TRANSFER CATALYSIS:

The term "phase transfer catalysis" (PTC) was coined by Starks\(^{86}\) in 1971 and became within a short period of time an active subject of research with deep implications especially in synthetic organic chemistry. Phase transfer catalysts are the substances which transfer a reactant frequently into an organic phase from aqueous phase across the interface in two phase heterogeneous solvent systems. PTC is thus concerned with conversions between chemical species situated in different phases.

PTC offers significant advantages over conventional procedures:

i) No need for expensive anhydrous or aprotic solvents.
ii) Improved reaction rates.
iii) Low reaction temperatures
iv) Easier work-up in many cases.

v) Aqueous alkali metal hydroxides replace alkoxides, sodamide, sodium hydride or metallic sodium.

There are other special advantages also, which are as follows:

i) Occurrence of reactions that would not otherwise proceed.
ii) Modification of selectivity.
iii) Change in product ratios. (e.g. O vs C alkylation)
iv) Increased yields through suppression of side reactions.

The original PTC mechanism for displacement reactions proposed by Starks\(^{87}\) is shown below. An ion pair, formed by extraction of anion \(Y^-\) into the organic phase by the onium salt cation \(Q^+\), undergoes a rapid displacement with \(RX\). The new salt \((Q^+X^-)\) then returns to the aqueous phase where \(Q^+\) picks up a new \(Y^-\) ion for the next cycle.

\[
RX + [Q^+Y^-] \rightarrow RY + [Q^+X^-] \quad \text{organic phase}
\]

\[
Na^+ \quad Y^- \quad Q^+ \quad X^- \quad \text{aqueous phase}
\]

\[
\text{inter phase}
\]

Scheme 1.1

Some of the common catalyst include quaternary ammonium and phosphonium salts,\(^{88}\) crown ethers\(^{89}\) and cryptands.

Tetra n-butyl ammonium chloride (\((nC_4H_9)_4N^+Cl^-\)), benzyl triethyl ammonium chloride \(PhCH_2(C_2H_5)_3N^+Cl^-\), aliquate 336 (tri-caprymethyl ammonium), tetra butyl phosphonium iodide (\((nC_4H_9)_4P^+I^-\)).
Typical inorganic sodium and potassium salts do not dissolve in nonpolar organic solvents. The same is true for salts of inorganic anions with small organic cations, (e.g. tetramethylammonium). Such ammonium salts often can be dissolved in dichloromethane and chloroform. The formation of ion pairs and their physical and chemical properties are strongly influenced by interaction with solvents.

Numerous PTC reactions have been reported. Some of them are listed below:

**Table 1.12 : Applications of PTC in organic synthesis.**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction</th>
<th>Phase Transfer Catalyst</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>N-alkylation of aromatic amine.</td>
<td>NBu₄X, EG ether</td>
<td>90</td>
</tr>
<tr>
<td>2.</td>
<td>β - elimination under basic conditions in inert solvent.</td>
<td>18 - Crown - 6</td>
<td>91</td>
</tr>
<tr>
<td>3.</td>
<td>Carbonylations of benzyl bromides.</td>
<td>TEBA</td>
<td>92</td>
</tr>
<tr>
<td>4.</td>
<td>Oxidation of secondary alcohol to ketone.</td>
<td>TDA-1</td>
<td>93</td>
</tr>
<tr>
<td>5.</td>
<td>Nucleophilic aromatic substitution reaction.</td>
<td>15-Crown-5</td>
<td>94</td>
</tr>
<tr>
<td>6.</td>
<td>Horner reaction.</td>
<td>NBU₄I</td>
<td>95</td>
</tr>
<tr>
<td>7.</td>
<td>Synthesis of aromatic ethers.</td>
<td>18-Crown-6</td>
<td>96</td>
</tr>
</tbody>
</table>

**1.4 Envirocats in organic synthesis.**

In modern synthetic methods the clean technology revolution provides enormous opportunities for chemist and chemical engineers to develop new, safer, more efficient and environmentally friendly chemical processes and products. Envirocats are unique supported reagent catalyst of low environmental impact,
which replace traditional processes associated with unacceptable level of waste and by products. Contract chemicals, England has developed following envirocats and have following physical properties as shown in Table (1.13).

Table 1.13: Envirocats and its physical properties.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Physical Properties</th>
<th>Envirocats EPZG</th>
<th>Envirocats EPZ10</th>
<th>Envirocats EPIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Appearance</td>
<td>Free flowing green powder</td>
<td>Free flowing green powder</td>
<td>Free flowing green powder</td>
</tr>
<tr>
<td>2.</td>
<td>Bulk density</td>
<td>0.76 g/cm³</td>
<td>0.55 g/cm³</td>
<td>0.7g/cm³</td>
</tr>
<tr>
<td>3.</td>
<td>pH of 2 % (w/v)</td>
<td>2.2</td>
<td>3.6</td>
<td>&lt;3</td>
</tr>
<tr>
<td>4.</td>
<td>Flamability</td>
<td>not flammable</td>
<td>not flammable</td>
<td>not flammable</td>
</tr>
<tr>
<td>5.</td>
<td>Surface area</td>
<td>250 m²/g</td>
<td>250 m²/g</td>
<td>250m²/g</td>
</tr>
<tr>
<td>6.</td>
<td>Acidic character</td>
<td>both Bronsted and Lewis acid</td>
<td>both Bronsted and Lewis acid</td>
<td>Bronsted acid</td>
</tr>
</tbody>
</table>

Acetalization of carbonyl compounds using Envirocat EPZG was successfully carried out by Bandgar et al. (Scheme 1.2).

\[
\begin{align*}
RCHO & \xrightarrow{(MeCO)_{2}O} (MeCO)_{2}O + Envirocat EPZG \\
 & \quad \xrightarrow{R \text{ reflux} 60-65^\circ C} R-COMe \\
R = \text{aryl, alkyl}.
\end{align*}
\]

Scheme 1.2

The Friedel-Crafts arylmethylation of phenol and anisole with various benzyl halides using Envirocat EPZ10 as a catalyst was successfully carried out by Bandgar et al.99

\[
\begin{align*}
\text{Cl} & + \text{R} \xrightarrow{EPZ 10 \text{ reflux}} \text{R} \\
X = \text{Cl, Br, NO}_2 \\
R = \text{OCH}_3, \text{OH}
\end{align*}
\]

Scheme 1.3
1.5.1 Introduction

Power ultrasound influences chemical reactivity through an effect known as cavitation which was characterised by Sir, John Thornycroft and Sidney Barby at the turn of the century. Cavitation is the formation and collapse of micro bubbles produced in a solvent medium while irradiated with ultrasonic waves. The term ultrasound refers to sound waves ranging in frequency from 20 KHz to 10 MHz. The most common technique to generate ultrasound is the use of transducer. The type of transducer used in most sonochemical equipment is based on the piezoelectric effect which was discovered by Currie brothers at the turn of century.

The use of ultrasound in chemical synthesis is very much on the increase due to some of its following features.

(i) Increased efficiency in mass transport.
(ii) Surface modification of reagents.
(iii) Enhancing the reactivity of biological materials

Thus, use of ultrasound provides in organic synthesis is one of the important alternative for increasing chemical reactivity.

There are five types of Sonicators which are generally useful for sonochemistry.

1. Cleaning bath
2. Probe system (including Cup-Horn and Flow Cell).
3. Submersible transducer.
5. Tube reactor.

The simple ultrasonic cleaning bath is by far the cheapest source of ultrasonic irradiation for the chemical synthesis (fig 1.5). In order to increase the amount of ultrasonic power available to reaction and to introduce the energy directly into the system, ultrasonic probe system is effective (fig 1.6)
Introduction

The use of ultrasound also enables reaction involving organometallic reagents to be carried out safely. The application of ultrasound to heterogenerous reaction involving solid phases has led to some spectacular rate enhancements.

1.5.2 Examples of reactions enhanced by ultrasound:

The following examples have been chosen to illustrate the potential for sonochemistry in chemical synthesis.

1) Rate acceleration in solvolysis.

With sonication the rate of this homogeneous hydrolysis can be increased by a factor of 20 at 10 °C in 50 % aqueous ethenol.\textsuperscript{101}

\[
\text{U.S.} \quad (\text{CH}_3)_3\text{CCl} + \text{H}_2\text{O} \rightarrow (\text{CH}_3)_3\text{COH} + \text{HCl}
\]

2) Particle size reduction and continuous surface cleaning.

The Ullmann coupling of 2-iodonitrobenzene to dinitrobiphenyl at 60 °C in dimethylformamide shows a 64 fold rate increase under sonication using substantially less metal in conventional methodology.\textsuperscript{102}

3) The avoidance of forcing conditions.

Classical methodology for the carbonylation reaction shown required both high pressures (200 atm.) and temperature (160 °C), using ultrasound these conditions can be reduced to only 4.4 atm. and 10 °C.\textsuperscript{103}

\[
\begin{array}{c}
\text{VCl}_3 \cdot (\text{THF})_3 \xrightarrow{\text{Cu/DMF}} \text{V(CO)}_6
\end{array}
\]
4) Simplification of procedure; safety considerations.

The copper powder requires an 8 hour reflux with potassium in THF but less 40 minutes by the sonochemicals route.\textsuperscript{104}

\[
\text{THF} \\
\text{CuBr}_2 + 2\text{Li} \quad \xrightarrow{\text{sonic}} \quad \text{Cu}^* + 2\text{LiBr}
\]

5) Change the reaction pathway.

In following example sonication impregnates the alumina surface with CN$^-$ ion and this masks the Lewis acid sites, so the reactions proceeds via nucleophilic displacement.\textsuperscript{105}

\[\text{CH}_2\text{Br} + \text{CH}_3\text{C}_6\text{H}_4\text{Br} + \text{KCN} + \text{Al}_2\text{O}_3 \xrightarrow{\text{sonic}} \text{CH}_3\left(\text{CH}_2\right)\text{C}_6\text{H}_4\text{I}\]

1.6 MICROWAVE ASSISTED ORGANIC SYNTHESIS
1.6.1 Introduction :\textsuperscript{106}

Microwave heating is very convenient to use in organic synthesis. The heating is instantaneous, very specific and there is no contact required between the energy source and the reaction vessel.

Microwave assisted organic synthesis is a technique which can be used to rapidly explore ‘chemistry space’, and increase in diversity of the compounds produced. In electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radiowaves. Microwaves have wavelength of 1mm-1m corresponding to frequencies between 0.3 and 300 GHz.

Inorganic chemistry, microwave technology has been used since the late 1970s, while it has been implemented in organic chemistry since the mid-1980s and the mid-1990s, however, the number of publications has increased significantly.

The short reaction times and expanded reaction range that is offered by microwave assisted organic synthesis are suited to the increased demands in industry.
In general most organic reactions have been heated using traditional heat transfer equipment such as oil baths, sand baths and heating jackets. These heating techniques are rather slow and a temperature gradient can develop within the sample. In addition, local overheating can lead to product, substrate reagent decomposition.

In contrast, in microwave dielectric heating, the microwave energy is introduced into the chemical reactor remotely and direct access by the energy source to the reaction vessel is obtained.

The reaction is often carried out in closed teflon vessel and in microgram scale. Teflon, polystyrene and glass are nearly transparent to microwaves.

1.6.2 Microwave assisted synthesis techniques:

i) Domestic household ovens: "Solvent-free" open vessel reactions. Most of the published chemistry has been performed using domestic microwave ovens. The key reasons for using a domestic household oven are that they are readily available and inexpensive.

ii) Reflux systems: A number of reflux systems have been developed in an effort to use solvents in microwave-assisted organic synthesis without the risk of explosion. Some systems are modified domestic ovens, while others have been designed with single mode cavities. The temperature cannot be increased by more than 13-26 °C above the normal boiling point of the solvent.

iii) Pressurized systems: Nowadays modern apparatus for running organic synthesis under pressure measurement, which avoids a great deal of the failures due to thermal runaway reactions and poor heating.

1.6.3 Dipolar polarization mechanism:

Ideally, to obtain a well defined heating pattern for small loads, a microwave apparatus utilising a single mode cavity is preferred. As the name implies, this type of cavity allows only a single mode to be present. A property designed cavity will prevent the formation of ‘hot and cold spots’ within the sample; resulting in a uniform heating pattern. This factor is very important when microwave technology is used in organic synthesis. For a substance to generate heat when irradiated with microwaves, it must possess a dipole moment. A dipole is sensitive to external electric fields and will attempt to align itself with the field by rotation (fig. 1.8).
Introduction

If two samples containing distilled water and tap water respectively, are heated in a single mode microwave cavity at a fixed radiation power and for a fixed time. The final temperature will be higher in the tap water sample this is due to the interaction of electric field component with the sample, the conduction mechanism. (fig. 1.8)

Numerous inorganic reagents have been reported for microwave assisted organic synthesis. Some of organic transformations carried by microwave irradiations are summarised in the following table.

**Table 1.14 : Microwave assisted organic transformations.**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Transamidation using KF supported alumina.</td>
<td>109</td>
</tr>
<tr>
<td>2.</td>
<td>Radical Michael addition reactions.</td>
<td>110</td>
</tr>
<tr>
<td>3.</td>
<td>Knoevenegel condensation using ZnCl₂ &amp; K-10 clay.</td>
<td>111</td>
</tr>
<tr>
<td>4.</td>
<td>1,3-dipolar cycloaddition using imidates.</td>
<td>112</td>
</tr>
<tr>
<td>5.</td>
<td>Protection and deprotection.</td>
<td>113</td>
</tr>
<tr>
<td>6.</td>
<td>Esterification of enols using Ac₂O, I₂.</td>
<td>114</td>
</tr>
<tr>
<td>7.</td>
<td>Synthesis of benzothiazine using EtOH-pyridine.</td>
<td>115</td>
</tr>
<tr>
<td>8.</td>
<td>Coumarin synthesis using pipidine.</td>
<td>116</td>
</tr>
<tr>
<td>9.</td>
<td>Synthesis of orthopthalic acid.</td>
<td>117</td>
</tr>
<tr>
<td>10.</td>
<td>Wittig reaction</td>
<td>118</td>
</tr>
<tr>
<td>11.</td>
<td>Synthesis of 5-Diaza-5, 8-Dihyropterins.</td>
<td>119</td>
</tr>
</tbody>
</table>

**fig.1.8:** Dipolar molecules which try to align with an oscillating electric field.
1.7 ORGANIC REACTIONS IN WATER

1.7.1 Introduction:

The use of water as a medium for organic reactions has a number of potential advantages:

i) It is the cheapest solvent available on earth.

ii) Isolation of the organic products can be performed by simple phase separation.\textsuperscript{120}

The use of water as solvent in organic chemistry was rediscovered in the eighties. During the proceeding decades, water as solvent was, for the most part, ruled out from the studies for several reasons. Among them were the insolvency of the reactants and the incompatibility of the intermediates with water. However, many biochemical processes occur in the presence of water, and the diversity of the reactions in water should prompt chemists to discover the potential of water, as a solvent. As a matter of fact, the hydrophobic effect, a principal force determining the folding of proteins and the binding of enzymes to substrate, was utilized for the first time in 1980 for a water promoted Diels-Alder reactions.\textsuperscript{121}

1.7.2 Structure of water:

Liquids (solvent) can be divided in two groups, in the first one, molecules are held together by weak non-directional Vander Waals forces and fill space in a regular manner. In these unstructured liquids, molecules have 10-11 nearest neighbors on average. The second group concern the structured liquid such as hydrogen bonds. In this case, molecules do not fill space efficiently and as a consequence, the structures liquids display cavities. To visualize the microscopic structure of liquid water, let us consider the hexagonal ice structure in which each water molecule shares four hydrogen bonds with its nearest neighbors. Such an extremely structured network of low entropy and low density displays many cavities which can easily accommodate solutes.\textsuperscript{122} In two state model, liquid water is represented as an equilibrium between such “structured water” constituted between ice type clusters and “unstructured water” having higher entropy and density in which each molecule has many more neighbors. This equilibrium can be influenced by temperature, pressure and additives. At room temperature and under normal pressure, water molecules in the pure liquid have 4.4 nearest neighbors. On averages as seen by neutron diffraction, the structure and the importance of water clusters are under investigation.\textsuperscript{123}
1.7.3 Reactivity of water:

Solvent effects are rationalized by studying the relative solvation of the initial (reactants) and transition states. This effect includes the solute-solvent interaction and the reorganization of solvent around the solute. It must be pointed out that there is no correlation between the structualization and the polarity of the solvents. Due to the hydrophobic interaction, they have a tendency to aggregate, but this association is not sufficient to explain the rate enhancement. Noteworthy is the high surface tension of water (72 dynes/cm), a consequence of its high c.e.d. (550 cal/cm³ or 22000 atm), which tends to induce a diminution of the surface of contact between hydrophobic and water molecule.

Following table lists some of the water promoted organic reactions.

Table 1.15: Water promoted organic reactions

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Type of reaction</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Michael-type reaction</td>
<td>124</td>
</tr>
<tr>
<td>2.</td>
<td>Reduction reaction using SmI₂ in water. Reduction of ketones as well as alkyl and aryl iodides.</td>
<td>125</td>
</tr>
<tr>
<td>3.</td>
<td>Decarboxylation of malonic acid derivatives in water under microwave irradiation.</td>
<td>126</td>
</tr>
<tr>
<td>4.</td>
<td>Stereoselective bromination of stilbene and chalcone.</td>
<td>127</td>
</tr>
<tr>
<td>5.</td>
<td>Preparation of ylidenemalononitriles without catalyst in water.</td>
<td>128</td>
</tr>
<tr>
<td>6.</td>
<td>InBr₃- water chemoselective dithioacetalization of aldehyde.</td>
<td>129</td>
</tr>
<tr>
<td>7.</td>
<td>Deprotection of alkyl TBS ethers.</td>
<td>130</td>
</tr>
</tbody>
</table>
N-halosuccinimides are active catalyst for the organic synthesis. The well known application of N-halosuccinimide is halogenations. Although radical halogenations often leads to mixtures of products, good yields of single products can be obtained by using N-halosuccinimide. For example a reagent that is more specific than $X_2$ for allylic and benzylic halogenations is N-halosuccinimide (NXS). An NXS reaction can be indicated by light or by some source of radicals, such as peroxide (ROOR).

\[
\begin{align*}
\text{Initiator} & \quad \overset{\text{CHCl}_3}{\text{NXS}} & \quad \text{Succinimide} \\
\text{N-halosuccinimide.}
\end{align*}
\]

Scheme 1.4

NXS acts as a halogenating agent by providing a low, but constant concentration of halogen, which is the halogenating agent.

The oxidation of organic substrates provides typically one-step routes to a wide range of important functionalized molecules including alcohols, aldehydes, ketones and carboxylic acid. Many traditional methods of oxidations involves aerobic oxidation, electrolytic oxidation, dehydrogenation by use of oxidizing agents.

The ambition of synthetic organic chemists is not satisfied by inventing oxidations that are occured due to a versatile oxidizing reagents, like air, oxygen, singlet oxygen, hydrogen peroxide and it's derivatives, organic peroxy acids etc.

For more demanding substrates, the use of stoichometric quantities or large excess of reagent is involved. Catalytic oxidation is an enormous subject, which has attracted the intrest of biochemist as well as organic, inorganic and physical chemist. Catalytic oxidations that operate, under neutral conditions and moderate temperatures and pressures are clearly desirable. Selectivity can often be critical importance, such as in the oxidations of polyfunctional substrates. The use of N-chlorosuccinimide, $C_4H_4ClNO_2$ and N-Bromosuccinimide, $C_4H_4BrNO_2$ as oxidizing agent is widely accepted.
NBS is used in the dehydrogenation of hydrazo compounds to azo compounds and in the oxidative degradation of α-hydroxy acids to aldehydes or ketones. This reagent also oxidizes alkyl trimethylsilyl to esters of ketones.

NCS either alone or in presence of dimethyl sulfide dehydrogenates alcohols to carbonyl compounds. Many organic transformations have been reported using N-halosuccinimide essentially under neutral conditions. Some of the applications of NBS & NCS in organic synthesis are summarized in the table (Table 1.16)

Table 1.16: Applications of NBS & NCS in organic synthesis

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction</th>
<th>Reagent</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Regioselective halogenation of activated pyridines.</td>
<td>NBS</td>
<td>134</td>
</tr>
<tr>
<td>2.</td>
<td>Oxidation of various alcohols to corresponding acrbonyl compounds.</td>
<td>NCS</td>
<td>135</td>
</tr>
<tr>
<td>3.</td>
<td>Chemoselective transesterification of β-keto esters.</td>
<td>NBS</td>
<td>136</td>
</tr>
<tr>
<td>4.</td>
<td>Preparation of Allylic trichlotins from α,α-diisoprophylhomoallylic alcohols.</td>
<td>NCS</td>
<td>137</td>
</tr>
<tr>
<td>5.</td>
<td>Synthesis of biaryls from arylzine iodides.</td>
<td>NCS</td>
<td>138</td>
</tr>
<tr>
<td>6.</td>
<td>One-pot synthesis of thiols from alcohols.</td>
<td>NBS</td>
<td>139</td>
</tr>
<tr>
<td>7.</td>
<td>Synthesis of aromatic ring fused cyclic 1,2-diketones, with one-carbon ring expansion.</td>
<td>NCS</td>
<td>140</td>
</tr>
<tr>
<td>8.</td>
<td>One-pot synthesis of aryl sulfones from alcohols.</td>
<td>NBS</td>
<td>141</td>
</tr>
<tr>
<td>9.</td>
<td>Methylation of silyl compounds.</td>
<td>NBS, NCS</td>
<td>142</td>
</tr>
<tr>
<td>10.</td>
<td>Bromination of hetrocyclic compounds.</td>
<td>NBS</td>
<td>143</td>
</tr>
<tr>
<td>11.</td>
<td>Conversion of aldeamines to amide using NBS / Hg (OAc)₂.</td>
<td>NBS</td>
<td>144</td>
</tr>
<tr>
<td>12.</td>
<td>Bromination and benzylation of heterocyclic carbonyl compounds.</td>
<td>NBS</td>
<td>145</td>
</tr>
</tbody>
</table>
Introduction

1.9 PERCHLORATE SALTS IN ORGANIC SYNTHESIS.

The chemical literature of the last ten years describes a growing arsenal of synthetic methodologies in which perchlorate salts dramatically affect yield, selectivity, reaction rate for key organic transformations. Following are the some commonly used perchlorate salts in organic synthesis:

i) Lithium perchlorate (LiClO\textsubscript{4}).
ii) Sodium perchlorate (NaClO\textsubscript{4}).
iii) Magnesium perchlorate (MgClO\textsubscript{4}).

Similar to perchlorate, applications of periodate salts are also equally important. Lithium perchlorate is a mild Lewis acid which affords almost neutral reaction conditions, in most of the organic reactions. Sauer\textsuperscript{146} was the first one to recognize the advantage of using a solution of 4M Lithium perchlorate in diethyl ether for carrying out Diel's-Alder reaction. The seminal contribution from Grieco and Cowoekers\textsuperscript{147} on the use of highly concentrated solution of lithium perchlorates in diethyl ether for synthetic transformations led to the reorganization of LPDE medium for various organic transformations. Anhydrous lithium perchlorate exhibits properties such as solubilities and reactivity in organic systems that are extraordinary even within the family of perchlorate salts. A viscous, saturated solution of LiClO\textsubscript{4} in diethyl ether was found to contain about 47% solute by weight. Viscosity may vary from 20-200 centipoises over the temperature range of 20 to 40°C. Several studies of mechanism that apply to the promotion of reactions by lithium perchlorate have generated interesting kinetic data. Reaction rate generally increases as solute concentration rises (in various solvents) and the metal ion acts as a Lewis acid character of the suspected Li\textsuperscript{+}/Et\textsubscript{2}O aggregate suggests a novel degree of sophistication of these chemistries. It will remain fertile area of research for many years.

\[
\begin{align*}
\text{BzCl, LiClO}_4 & \quad 250, 7h \\
\text{OH} \quad \rightarrow \quad \text{OBz}
\end{align*}
\]

Bandgar et al\textsuperscript{148} reported that selective benzylation of primary alcohol with catalytic amount of lithium perchlorate in THF under mild condition.

Sodium Perchlorate (NaClO\textsubscript{4}) is highly accepted salts in organic synthesis. The development of novel chemistries involving perchlorate salts in organic media has accelerated to the point where a systematic examination of these reaction
systems is not only justified but also imperative. There is an enormous scope in utilizing the alkali and alkaline earth metal salts that are soluble in organic solvents as Lewis acids to carry out synthetic transformations, with respect to the modulation of the Lewis acidity of sodium ion, sodium perchlorate plays an important role in organic reactions under essentially neutral conditions.

To achieve selectivity in Lewis acid catalyzed reactions, there is an enormous scope in utilizing NaClO₄ in organic synthesis. Apart from the acceleration of the rate of the reaction, high chemo-, regio-, and stereoselectivities have been observed by many of the examples. The reactions are generally carried out under mild, essentially neutral and simple work-up conditions, which makes sodium perchlorate reagent highly desirable and useful to synthetic organic chemists.

Some of the application of perchlorate salts in organic synthesis are summarised in Table 1.17.

**Table 1.17**: Application of perchlorate salts catalysed organic synthesis.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Chemoselective dithioacetalization of aldehydes and acetals.</td>
<td>149</td>
</tr>
<tr>
<td>2.</td>
<td>Michael addition reaction.</td>
<td>150</td>
</tr>
<tr>
<td>3.</td>
<td>Chemoselective substitution of acetals with silyl enol ether.</td>
<td>151</td>
</tr>
<tr>
<td>4.</td>
<td>Rearrangement of epoxide to carbonyl compounds.</td>
<td>152</td>
</tr>
<tr>
<td>5.</td>
<td>Synthesis of α-hydrazinophonates from aldehydes.</td>
<td>153</td>
</tr>
<tr>
<td>6.</td>
<td>Acetylation of alcohols</td>
<td>154</td>
</tr>
<tr>
<td>7.</td>
<td>Electrochemical formation of glycals in THF</td>
<td>155</td>
</tr>
</tbody>
</table>
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1.10 REFERENCES:


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42. M. A. Zolfigol, A. Bomoniri, Synlett., 2002, 10, 1621.

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