CHAPTER - I
INTRODUCTION

Quite incongruous to the well known addition of halogens to the double bond, it was only in 1919 that the first report by Whol appeared on an apparently general method for the direct introduction of a halogen atom (bromine) in the "allylic position" of an alkene:

\[ X_2 \quad \xrightarrow{\text{--CH=CH--CH\text{H}_2--}} \quad \text{--CH=CH--CHX--} \]

rather than

\[ \text{--CHX--CHX--CH\text{H}_2--} \]

The work was not given due attention for long. In 1942, Ziegler and coworkers published their extensive research on the allylic bromination of alkenes, in which they introduced the unique brominating agent N–bromosuccinimide (NBS). Ziegler and coworkers (1942) prepared besides NBS, eight other N–bromoimides or bromoamides but found them to be far less satisfactory than NBS for allylic bromination. The reaction of allylic bromination is known as Wohl–Ziegler reaction. The outstanding brominating ability of NBS is due to four fundamental properties.

1. An almost nonpolar N–Br bond, following homoloytic fission to give a Br atom.

2. Good agreement between the NBr–CO bond distance in NBS and the C= C distance in alkenes and aromatic compounds.

3. Similarity between the valency angles in

\[ \text{CO–N} / \text{Br} \quad \text{and} \quad \text{CH}_3 / \text{C}={\text{C}} \]
4. Planar structure of the NBS molecule as a prerequisite for an exchange reaction at the surface of the NBS crystal lattice.

The N-haloamides or imides are generally named by putting the prefix, e.g., N-bromo, before the name of the parent amide or imide. In Chemical Abstracts, N-Bromosuccinimide has been listed as a derivative of 2,5-pyrrolidinedione, i.e., 1-bromo-2,5-pyrrolidinedione.

\[
\begin{array}{c}
\text{CH}_2\text{CO} \\
\text{CH}_2\text{CO} \\
\text{NBr}
\end{array}
\]

A variety of N-haloamides or imides useful for allylic bromination and oxidation of organic compounds may be represented in the following table:

### N-Haloamides and Imides

<table>
<thead>
<tr>
<th>Name and formula</th>
<th>Active Hydrogen %</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Bromoacetamide (NBA) CH$_2$CONHBr</td>
<td>58.0</td>
<td>Wohl and Jaschionowski,(^{(13)}) Park et al.(^{(14)}), Buckles at al.(^{(15)})</td>
</tr>
<tr>
<td>N-Bromoacetanilide CH$_2$CONBrC$_6$H$_5$</td>
<td>37.4</td>
<td>Ziegler et al.(^{2})</td>
</tr>
<tr>
<td>N-Bromobenzamide C$_6$H$_5$CONHBr</td>
<td>40.0</td>
<td>Ziegler et al.(^{2})</td>
</tr>
<tr>
<td>N-Bromobenzenesulphonic acid C$_6$H$_5$SO$_2$NHBr</td>
<td>33.9</td>
<td>Ziegler et al.(^{2})</td>
</tr>
<tr>
<td>N-Bromocarbamide H$_2$NCONHBr</td>
<td>57.2</td>
<td>Kiss,(^{58})</td>
</tr>
<tr>
<td>N-Bromosuccinimide</td>
<td>44.9</td>
<td>Ziegler et al.(^{2})</td>
</tr>
<tr>
<td>Compound</td>
<td>Value</td>
<td>Reference</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------</td>
<td>-----------------</td>
</tr>
<tr>
<td>N-Bromoglutaramide</td>
<td>41.6</td>
<td>Ziegler et al. 2</td>
</tr>
<tr>
<td>N-Bromophthalimide</td>
<td>35.4</td>
<td>Ziegler et al. 2</td>
</tr>
<tr>
<td>N-Bromosaccharin</td>
<td>30.5</td>
<td>Bachhawat and Mathur 35</td>
</tr>
<tr>
<td>N-Chloroacetamide</td>
<td>38.0</td>
<td>Saigusa et al. 6</td>
</tr>
<tr>
<td>CH\textsubscript{3}CONHCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Chlorosuccinimide</td>
<td>26.4</td>
<td>Lambert et al. 39</td>
</tr>
<tr>
<td>CH\textsubscript{2}=C=NO\textsubscript{2}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Chloroacetanilide</td>
<td>20.8</td>
<td>Ingold; 60 Banthorpe. 61</td>
</tr>
<tr>
<td>CH\textsubscript{3}CONClC\textsubscript{6}H\textsubscript{5}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Chlorophthalimide</td>
<td>19.5</td>
<td>Djerassi. 62</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}CO\textsubscript{2}NCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Iodosuccinimide</td>
<td>56.4</td>
<td>Djerassi and Lenk. 63</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}CO\textsubscript{2}NI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The electronegativities of bromine, nitrogen, and oxygen are 2.74, 3.07 and 3.50 respectively, on Pauling’s electronegativity scale. Thus the bromine when
linked to oxygen or nitrogen acquires a positive oxidation state. The electronegativity of nitrogen is further increased by linking it to certain electron withdrawing groups, e.g., acyl groups. Thus N-substituted haloimides are known as "positive halogen compounds".

The N-Br bond in NBS is essentially covalent. The acidic character of succinimide\(^{(1,3)}\) is accounted for by the stabilization of the anion\(^{(2)}\) in which charge dispersion, rather than charge separation, can take place. Similarly, the contribution of an ionic form of NBS, particularly in solution in polar solvents cannot be ruled out. It also follows that the greater the electronegativity of the nitrogen atom, the more positive the halogen, which consequently is a stronger oxidant.

The reactants of NBS may be broadly classified into four types:

1. Allylic or benzylic bromination reactions.
2. Oxidation reactions.
3. Aromatization reactions (Dhydrogenations).
4. Addition to the alkene double bond.

(i) **ALLYLIC OR BENZYLIC BROMINATION**

It has long been known that CCl\(_4\) is particularly suitable medium for allylic bromination.\(^{(2)}\)

The present knowledge reveals nothing regarding the action of NBS on saturated aliphatic hydrocarbons. Alicyclic hydrocarbons such as cyclohexane and decalin undergo bromination in the presence of free radical initiators. Cyclohexane is converted into monobromide and decalin into 1,4,5,8-tetabromo-9,10-octalin via 9-bromodecalin and 9,10-octalin.\(^{(2,5)}\)

Mono and dialkenes were thoroughly investigated by Ziegler et al.\(^{(2)}\) According to them, methylene groups in the allyl position are more readily
brominated by NBS than methyl groups and these more readily than methyldyne groups. However, this order largely loses its validity, if activators are used. Straight chain and branched alkenes can only be monobrominated in one allyl position by NBS irrespective of the location of double bond. Thus allyl bromide, for example, cannot be brominated further. On the other hand, one double bond renders up to a maximum of four allyl positions susceptible to attack by NBS, as could be shown in the case of tetramethyl ethane and 9,10-octalin. Certain dialkenes exhibit peculiar behaviour under the action of NBS. Thus diallyl and 2,3-dimethylbutadiene undergo bromination in only one allyl position, accompanied by a partial allylic rearrangement.

Allycyclic compounds were also thoroughly examined. The same rules apply to the cycloalkenes as to the alkenes, methylene groups react more readily than methyl groups. The second bromination invariably occurs in the same ring, namely in the second, as yet free, allyl position. Only in the event of latter's being occupied are other allyl positions in different rings brominated. Cyclic alkenes can be dibrominated in one allyl position by NBS. These products are thermolabile, however, and cannot be isolated as they undergo an allylic rearrangement and HBr elimination to give stable end products. Cyclohexene forms meta and para dibromobenzenes. Tetralin gave the extremely thermolabile 1,1,4,4-tetrabromide which was isolated and readily aromatized to 1,4-dibromonaphthalene via a double HBr elimination. 1,5-Cyclooctadiene behaves similarly to diallyl; it undergoes a double allylic rearrangement to give 1,4-dibromo-5,7-cyclooctadiene. Cyclooctatetraene behaves like an aromatic compound and does not react with NBS in the absence of activators.
(ii) AROMATIC COMPOUNDS

NBS fails to attack benzene. It brominates naphthalene in position 1 and anthracene and phenanthrene at position 9. In methylated or highly alkylated aromatic compounds, the $-\text{CH}_3$ or $-\text{CH}_2-$ group, respectively, corresponds to the allyl positions. This “benzyl position” is generally more activated by the aromatic nucleus than most other allyl positions. In this class of compounds NBS also reacts more readily with $-\text{CH}_2-$ group than with $-\text{CH}_3$ or $-\text{CH}_2-$ groups, here also the differences in activity are affected by the use of activators. Thus under the action of NBS, toluene and 1- and 2-methylnaphthalene will add up to two bromine atoms in the methyl group before side reactions are observed. If an alkyl group is activated by several phenyl rings, the bromination proceeds readily. This is found in the reaction with diphenyl and triphenyl methane and fluorine. If longer alkyl chains are present, the bromides readily undergo HBr elimination to form a double bond, as is illustrated by 2-ethylnaphthalene. In ortho, meta and para dimethyl (allyl) aromatic compounds, one to four atoms of bromine may be introduced depending on the choice of reaction conditions. NBS only introduces one bromine atom into sterically unfavourable position. Compared to orthoxylene benzocyclobutene is only slightly less readily monobrominated by NBS.\(^{(2,17,18)}\) The ability to undergo bromination increases sharply from indane to tetralin and 9,10-dihydroanthracene. Tetralin yields a stable dibromide, while the tetrabromide decomposes to 1,4-dibromonaphthalene at room temperature. No intermediate can be isolated in the case of 9,10-dihydroanthracene, a 9-bromo or 9,10-dibromoanthracene is obtained, depending upon the amount of NBS. The elimination of HBr from thermolabile bromides resulting in the aromatization was used as a synthetic method by Barnes et al.\(^{(5,19)}\) Thus the monobromides of dibenzyl and acenaphthene lose HBr to form stilbene and acenaphthylene. Indene and propenyl benzene
undergo bromination with NBS with extreme difficulty and thus are exception, 1,2- and 1,4-dihydronaphthalene react readily with two moles of NBS. The thermolabile monobromides undergo HBr elimination to give equal amount of naphthalene and 3,4- or 2,3-dibromotetralin respectively.\(^{(20)}\)

Phenols depending upon the reaction conditions yield different products. They yield generally the para substituted compounds, with large amount of NBS, highly substituted brominated compound is obtained.\(^{(3,11,22)}\) Hydroquinone with NBS in water\(^{(46)}\) or even in presence of dimethylformamide\(^{(64)}\) undergoes dehydrogenation forming quinone. Ortho chlorophenol\(^{(20)}\) gives 2-chloro-4,6-dibromophenol, 2,3-Dimethylphenol\(^{(23)}\) with equimolar NBS in CCl\(_4\) given 2,3-dimethyl-4-bromophenol in 20% yield. The reaction is completed in 8 minutes. Addition of benzoylperoxide\(^{(23)}\) did not alter the reaction time. With two mole\(^{(21)}\) of NBS 80.0% of 2,3-dimethyl-4,6-dibromophenol is obtained after 15 minutes. One mole of 3,4-dimethylphenol\(^{(23)}\) with one mole of NBS gives 25.0% of 2-bromo-4,5-dimethylphenol, with two mole\(^{(23)}\) of NBS 2,6-dibromo-3,4-dimethylphenol is produced. Thus nuclear bromination of xylenols follows the same rules as for aromatic substitution with elemental bromine.\(^{(2)}\)

Wohl\(^{(1,3)}\) found that N-bromoacetamide (NBA) reacts with anisole in presence of catalyst in long time. Buu-Hoi\(^{(24)}\) found that no catalyst is required with NBS while reacting with phenolic ethers though several hours are required for completion of the reaction. In case of \(\alpha\)- and \(\beta\)-naphthol ethers\(^{(24)}\) reaction takes place in few minutes. Kornev et al.\(^{(25)}\) found that bromination with the help of NBS is considerably accelerated by the use of free radical generator (diazonomobenzene) in the case of anisole, phenetole, veratrole, dimethyl ether of hydroquinone. Very little is known about the reaction between NBS and tertiary
aliphatic amines in an anhydrous medium. Dunstan and Henbest\textsuperscript{(26)} observed an oxidative dealkylation to the aldehyde and the secondary amine in aqueous dioxane through the intermediate enamine step. Among the mixed substituted aliphatic aromatic amines, only N–dimethyl aniline and acetanilide were investigated.\textsuperscript{(21)}

Tertiary and secondary aromatic amines can be brominated in para position with high selectivity and in good yields.\textsuperscript{(2)} The reaction of only simple heterocyclic compounds have been studied with NBS. Pyridine\textsuperscript{(27)} gives 3,5–dibromo derivative, while picolines, quinaldine and lepidine remain unattacked with NBS even after prolonged boiling with NBS. According to Hasogawa\textsuperscript{(28)} bromination of methyl group is possible if activator like dibenzoylperoxide is used. The N–oxides of the heterocycles are similarly brominated in the methyl groups by NBS with the help of free radical generator.\textsuperscript{(2,28)} The directing effect of the free radical initiator is clearly evident in the reaction of NBS with 2– and 3–methylfuran and corresponding thiophenes\textsuperscript{(29,30)} depending upon the reaction conditions, bromine is introduced either in the side chain or in the ring. NBS reacts with indole, 2,3–benzofuran and 2,3–benzothiophene in the β–position. The reaction is through free radical. Reactions with pyrimidine,\textsuperscript{(31)} uracil,\textsuperscript{(32)} thiazoles,\textsuperscript{(33)} imidazoles\textsuperscript{(33)} and coumarins\textsuperscript{(29)} have also been studied. Carbazoles\textsuperscript{(35)} behave like aromatic amines in this reaction and are brominated in the para position with respect to nitrogen.

The substituents also affect the rate of reaction, for example, a –CH\textsubscript{2}– group is least activated by the presence of the methyl group and is most activated in the vicinity of carbonyl group. The order of reactivity is shown below:

\[
X= \text{CH}_2 \text{–R} \quad (R = \text{H or alkyl})
\]
\[
X= \text{CH}_2 < \text{C–C} < \text{R}_3\text{N} < \text{OR} < \text{CO}
\]

This series, however, loses all validity in the presence of free radical generators.
(iii) **OXIDATION**

A large number of organic "psotive" halogen compounds have been used for the oxidation of a variety of organic compounds.\(^{34}\) The oxidation reactions of NBS and other related compounds involved the abstraction of hydrogen from C–H, O–H, N–H, S–H bonds and in some cases the addition of oxygen has also been observed. Although hypobromite solutions have generally been used to bring about such oxidations but NBS is advantageous due to the following reasons:

1. NBS is more stable in neutral, aqueous or slightly acidic buffer medium and can, therefore, be used for oxidation at relatively lower pH while in these conditions hypobromites are unstable.

2. NBS serves as a sources of brominium ion or hypobromite of low concentration and the reaction is free from side reaction generally associated with the use of hypobromite solutions. NBS is available in high state of purity and can be used as a primary standard.

3. A number of analytical methods and indicator systems are available for determining NBS in reactions involving excess of the reagent, as well as for its determination in the direct titration. In oxidation reaction NBS undergoes a simple two electrons reduction to give bromide ion and succinimide as products which do not interfere in the determination of organic compounds.

   There is large evidence that in polar media the oxidation proceeds through a positive halogen which is accepted to be the attacking species. However, NBS may also be slowly hydrolysed to hypobromite. Even the molecular NBS or molecular bromines may act as reacting species. A variety of reaction conditions have been used to affect such oxidation and the ease of reactions and the selectivity is often dependent on the solvent, pH of the medium and other reaction conditions.
(iv) **ALCOHOLS**

NBA was used in the oxidation of the secondary alcohols to ketones in aqueous acetone by Reich and Reichstein.\(^{(35)}\) Fieser and Rajgopalan\(^{(16,37)}\) studied the oxidation of steroidal alcohols by NBS and also established its stereoselectivity in the oxidation of steroid alcohols.\(^{(38)}\) The mechanism of oxidation of alcohols with NBS is not clear. Kruse et al.\(^{(39)}\) proposed a possible mechanism shown below:

\[
\text{C-CH}_2\text{OH} \xrightarrow{\text{NBS}} \text{C-CH}_2\text{OBr} \rightarrow \text{C-\text{CO} + HBr}
\]

The fact that ethylbenzylether, which cannot form a hypobromite, is oxidized by NBS to a benzaldehyde, rules out the above mechanism. Lecomte and Gaunt\(^{(41)}\) suggest that oxidation takes place via substitution by bromine of a hydrogen on the carbon atom bearing the \(-\text{OH}\) group and then subsequent rapid loss of hydrogen halide.

\[
\text{C-\text{O}H} \xrightarrow{\text{NBS \text{slow}}} \text{C-\text{Br}} \rightarrow \text{C-\text{CO} + HBr \text{fast}}
\]

Langbein and Steinert\(^{(41)}\) while studying the kinetics of oxidation with NBS found that the oxidation is brought about by molecular bromine formed by an autocatalytic reaction as shown below:

\[
\text{CHOH} + 2 \text{NBr} \rightarrow \text{C-O} + 2 \text{NH} + \text{Br}_2
\]

Venkatsubramanian et al.\(^{(42)}\) proposed a cyclic transition state for the oxidation of alcohols with NBS.
Secondary alcohols\(^{(66)}\) are oxidized easily while tertiary alcohols\(^{(39)}\) are more or less resistant to oxidation with NBS. Certain other positive halogen containing compounds, e.g., N-bromocaprolactam,\(^{(43)}\) N-chlorosaccharin\(^{(44)}\), N-bromosaccharin\(^{(45)}\) have been found to be quite effective for the oxidation of alcohols.

(v) **CARBOXYLIC ACIDS**

Akanoic acids except formic acid are resistant to oxidation with NBS. Formic acid\(^{(46)}\) and oxalic acid\(^{(47)}\) are completely oxidized by NBS in aqueous solution forming carbon dioxide, HBr and succinimide. Maleic acid\(^{(48)}\) and fumaric acid\(^{(48)}\) gave acetaldehyde, CO\(_2\) and HBr. \(\alpha\)-Hydroxy acid\(^{(49)}\) undergoes oxidative decarboxylation producing aldehydes and ketones having one carbon atom less than the parent acid. Phenylacetic acid\(^{(50)}\) in CCl\(_4\) with NBS gives benzaldehyde. Its mechanism is not very clear.

(vi) **NITROGEN COMPOUNDS**

Aliphatic primary and secondary amines\(^{(50)}\) readily form N-bromo derivatives with NBS followed by the elimination of HBr. Tertiary amines\(^{(50)}\) undergo C–N bond fission forming aldehydes and secondary amines. The reaction mechanism\(^{(26)}\) of bond fission is not very clear. Hydrazine\(^{(51)}\) and its derivatives yield nitrogen with NBS at room temperature and this reaction is used for its quantitative determination. Aryl hydrazines\(^{(57)}\) also give nitrogen along with hydrazobenzenes. Some important applications\(^{(51)}\) based on the determination of hydrazine function consists in the determination of isonicotinic acid hydrazide, the well known antituberculosis drug\(^{(55)}\) and semicarbazide. The molecular weight of the carbonyl compounds have also been determined by converting them to their semicarbazones with subsequent determination of the semicarbazide obtained by their hydrolysis.
(vii) **SULPHUR COMPOUNDS**

Thiols are oxidized by NBS in CCl₄ to the corresponding disulphides\(^{56-60}\). The same oxidation products are formed by oxidation in aqueous acetic acid medium.\(^{61-65}\) In aqueous HCl medium both thiols\(^{66}\) and disulphides\(^{67}\) are oxidized to the corresponding sulphonic acids while the thioether group in methionine is oxidized to the sulphone. Thiourcas\(^{68-73}\) and thioamides\(^{74-85}\) in presence of sodium bicarbonate are oxidized to sulphates. Tiwari and Pandey\(^{57}\) have found that sulphur is formed when the reaction is carried out in solutions in the absence of sodium bicarbonate.

(viii) **PRESENT WORK**

In the present investigations, the author has studied the bromination of phenols and their methyl ethers with NBS in presence of varying amount of catalyst in different solvents (CCl₄ and acetic acid). The results obtained have been incorporated in chapter two of the thesis.

Chapter three deals with the bromination of acetophenones and their methyl and nitro derivatives in different solvents. The effect of catalysts on bromination of above mentioned compounds have also been studied.

In chapter four the bromination of 2-hydroxyacetophenone, 4-hydroxy acetophenone, 2,4-dihydroxyacetophenone, 2,5-dihydroxyacetophenone and their methyl ethers with NBS in presence of different solvents with benzoyl peroxide and anhydrous aluminium chloride as catalysts have been reported.

Finally the results have been discussed from the point of view of mechanism operative in bromination by NBS under various sets of conditions.
CHAPTER 1

REFERENCES


