Chapter 1

INTRODUCTION

The acetal research has contributed much towards the synthesis of catalytic antibodies\(^1,2\), oligonucleotides\(^3\) and hypolipidemic agents\(^4\). Acetals are also used to analyze plasmalogens\(^5,6\), riboacetal internucleotide linkage\(^7\), lipase catalyzed selective deacetylation\(^8\), biomechanical aspects of bone and interface reactions\(^9\) and stereochemical structures of synthesized and natural plasmalogalactosyl ceramides from equine brain\(^10\). Acetals play a vital role in bio-organic research in exploring anti-malarial\(^11\), anti-viral\(^12\), anti-bacterial\(^13\), anti-inflammatory\(^14\), anti-tumor\(^15\) and anti-cancer\(^15\) activities. The studies of enzymes\(^16\), thrombin inhibitors\(^17\), ADP-ribose linkages to proteins\(^18\), bio-prosthetics devices\(^19\) and knee-replacement\(^20\) have been made through the investigation of acetals.

It is known that acetals are susceptible to addition\(^21\), oxidation\(^22\), reductions\(^23,24\), rearrangements\(^25,26\), condensations\(^27\), and hydrolysis\(^28\) in the presence of catalysts. Acetal derivatives of aldehydes are valuable in synthesis either as intermediates or as protecting groups\(^29,30\). The literature contains a few references on the preparations\(^31,32\) and reactions\(^33,34\) of aromatic and heteroaromatic acetals resulting in synthetically important compounds as the major products\(^35,36\).
But the literature lacks detailed study on the action of halocompounds on aromatic and heteroaromatic acetals especially at very low temperature.

Titanium tetrachloride and its alkoxy derivatives have been used in many reactions. The use of titanium chloride and stannic chloride in organic reactions is of relatively recent origin. The work of Mastagli and Gnanadickam on the action of titanium tetrachloride on the aliphatic acetals has revealed that it could bring about a rearrangement which till then had not been reported. Further, the work of Mastagli and Yves proved conclusively that titanium alkoxides could catalyze the Meerwein-Ponndorf-Verely type of reduction. They separately prepared the various alkoxy derivatives like TiCl$_3$OBu, TiCl$_2$ (OBu)$_2$ and Ti(OBu)$_4$ by following the procedure of Freidлина and Nesmeyanov and conducted the reaction.

The pioneering work done by Mastagli and Gnanadickam on the rearrangement of aliphatic acetals catalyzed by titanium tetrachloride has been extended to aromatic system by Arulraj. Meerwein and Schmidt were probably the first to study the reaction of aromatic acetal on ThO$_2$, but they did not pay much attention to the mechanistic aspect.
In 1976, Fleming and Bolker studied the reduction of some cyclic acetals with Co$_2$(CO)$_8$ catalyst and they reported aromatic ethers and alcohols as the major products and proposed mechanisms for the reactions. Recently Morris Don has disclosed some features regarding the reactions of aromatic acetals over Pt/C catalyst, aromatic ester being the major product.

Two of the well-known organic reactions are the Friedel-Crafts acylation and alkylation in which aluminium bromide has a long history as an exceedingly active catalyst. Halides, alkoxides, alkoxy halides and alkyl halides of metals like aluminium, boron, tin, titanium, vanadium and iron are used in many organic reactions. The Meerwein-Ponndorf-Verely reduction of carbonyl compounds involves aluminium alkoxide as the reagent.

It was discovered independently by Verely and by Meerwein and Schmidt and the reaction involves the transfer of one valence bond of the aluminium and one hydrogen atom from the alkoxide to the carbonyl compound accompanied by the bond formation between the newly formed alcohol and aluminium. In 1926, Ponndorf reported that the reaction could be made more general by employing the aluminium derivatives of the more easily oxidisable secondary alcohols. The aluminium isopropoxide reduction has been carried out with aliphatic and aromatic aldehydes and
ketones. Since the reducing agent is specific, other groups susceptible to reduction are not affected. Although a number of metals have been used as their alkoxides for reduction, the aluminium derivatives have been found to be the best reagents.

They have the advantages of being much weaker condensing agents than sodium or magnesium alkoxides and are soluble in both alcohol and hydrocarbons. Recently the use of aluminium alkoxide in promoting the hydride-transfer reactions has been reviewed by Deno et al. They have reported that the efficiency of aluminium alkoxide in promoting hydride-transfer reactions might be due to their activation of both hydride donor and the hydride acceptor nature. The aluminium alkoxides with their open sextet of electrons would coordinate with the carbonyl oxygen. Concomitantly the aluminium alkoxide possesses more of a negative charge on the alcohol oxygen than the free alcohol and this facilitates the departure of the hydride.

The reactions of aliphatic acetals catalyzed by solid acids have been extensively studied by various researchers and in most cases synthetically important α, β-unsaturated ethers have been obtained as the major products. Klein (1954) got a good yield of alkyl vinyl ether by passing aliphatic acetal over barium oxide on silica gel at elevated temperatures.
Hagemeyer and Perry (1957) obtained aldehyde as one of the major products in the study of aliphatic acetals\textsuperscript{48} catalyzed by alumina. In 1967 Michitoshi \textit{et al.}\textsuperscript{49} found out that metal sulphates supported on γ-alumina could act as an effective catalyst for the formation of ethyl vinyl ether from acetaldehyde diethylacetal. They suggested acid-catalyzed mechanism for the reaction and ruled out the thermal decomposition of acetal under their experimental conditions.

Makin \textit{et al.}\textsuperscript{50} (1976) obtained the corresponding unsaturated ether during their study on cyclohexylcarbaldehyde acetal over ammonium dihydrogen phosphate. Similarly on sodium hydrogen sulphate catalyst\textsuperscript{51} Coburm (1977) got 92 percent unsaturated ether from nitro substituted aliphatic acetal.

Xavier and Arulraj\textsuperscript{27} have reported that when aromatic acetals in vapour phase were passed over γ-alumina, the product mixture was found to contain ester, ether and aldehyde of aromatic nature.

Studies made by Angayal and James\textsuperscript{52} have shown that acetals are not very resistant to oxidative cleavage as they are generally believed to be. Oxidation of acetals by different reagents has been carried out. They have shown that chromium trioxide in acetic acid oxidizes acetals $R_1CH(OR_2)(OR_3)$ and aldehydes to
esters, $R_1^1COOR^2$ in which one of the alkoxy groups constituting the acetal has been retained whilst the other is usually oxidized to a ketone. These authors have found that glycosides being acetals are oxidized according to the general scheme, the glycon being retained and the ring being ruptured.

Kinetic study of oxidation of acetals and substituted aromatic acetals$^{53}$ by chromic acid in aqueous acetic acid medium yielded the corresponding aromatic esters as the main product.

Electrochemical oxidative studies on aromatic acetals in acetonitrile medium have been reported by Krishnamoorthy and Arulraj$^{54}$. Under electrical field, with the help of a radical obtained from a supporting electrolyte, acetals were found to yield aromatic esters.

Dichlorine monoxide, a powerful and selective chlorinating agent$^{55}$ has been used for either side chain or ring chlorination of deactivated aromatic substrates and it gives excellent yields under mild conditions.
The electrophile produced from Cl₂O has limited stability at room temperature and has not been characterized.

The chlorination of anisole by hypochlorous acid⁵⁶ has been studied in which the chloronium ion, Cl⁺ is the attacking species. The intermediate found is a sigma complex of the type shown below.

![sigma complex](image)

Many N-halocompounds are used as important reagents in organic chemistry. The N-halocompounds such as N-chloroamines, N-chlorophthalimide, N-chlorosuccinimide, N-chlorohydantions, N-chlorocaprolactam, N-chlorobenzamide, N-chlorosaccharin and N-chloropiperidone have already been used in the oxidation reactions. The study of kinetics involving N-halocompounds has led to the mechanism of their action.

The pioneering work done by Pause and Kamat⁵⁷ reveals the use of N,N-Bismorpholinophosphinic chloride as the coupling reagent for the first time in the peptide synthesis. Chlorination of alkanes by N-chlorophthalimide⁵⁸ has been studied. The mechanism is of free radical type. It is used as a powerful chlorinating agent. It is well known that N-haloamides⁵⁹ in the
presence of halogen acids give rise to free chlorine and thus show specific halogen acid catalysis.

Singh et al.\textsuperscript{60} studied the kinetics and mechanism of oxidation of some cyclic ketones by N-bromoacetamide. The kinetics of oxidation of cyclopentanone and cyclohexanone by N-bromoacetamide were also investigated in perchloric acid (HClO$_4$) medium in the presence of mercuric acetate.

Rawat and Agarwal\textsuperscript{61} have reported the oxidation of ascorbic acid by N-chlorobenzamide in 30 percent methanol. The oxidation of ascorbic acid by N-chlorobenzamide is strongly catalyzed by hydrochloric acid. Rawat and Agarwal\textsuperscript{62} have investigated the kinetics of oxidation of hydrazine and hydroxylamine by N-chlorobenzamide in hydrochloric acid medium. The reaction shows independent nature to the reducing substrates. Rawat and Agarwal\textsuperscript{63} reported the kinetics of oxidation of aniline, ortho and meta-toluidine by N-chlorobenzamide in acid medium.

Bachhwat et al.\textsuperscript{64} have reported that N-chlorosaccharin could be used as an oxidizing agent. They have oxidized many organic substances with N-chlorosaccharin. 1-Chlorobenzotriazole has been extensively used both in chlorination and oxidation of many organic substrates.
Oxidation of variety of alcohols, hydrazo compounds, 1,1-disubstituted hydrazines and ethers with 1-chlorobenzotriazole were done by Res and Storr\textsuperscript{65,66}.

Chlorination of aromatic compounds has also been done with 1-chlorobenzotriazole\textsuperscript{67}. Kingsbury and Johnson\textsuperscript{68} have studied the chlorination of organic compounds by chlorobenzotriazole. Berti \textit{et al.}\textsuperscript{69} carried out the chlorination of substituted indoles with 1-chlorobenzotriazole and they have reported that only 3-position of the indole ring was chlorinated.

Gurumurthy \textit{et al.}\textsuperscript{70} investigated the chlorination of some substituted 4-piperidones by chlorobenzotriazole in aqueous acetic acid medium at 303 K. The product was identified as 2-chloro-4-piperidone and benzotriazole.

Trost and Tamaru\textsuperscript{71} studied the oxidative decarboxylation of \(\alpha\)-methylthiocarboxylic acids.

They reported that \(\alpha\)-methylthiocarboxylic acid could be decarboxylated to the corresponding ketones with N-chlorosuccinimide in an alcohol solvent.
Samuel and Reed\textsuperscript{72} studied the reaction of alkynes with N-chlorosuccinimide in the presence of methanol.

They reported that two moles of CH\textsubscript{3}OCl can be added to triple bonds. N-bromosuccinimide does not oxidize aliphatic primary alcohols but N-chlorosuccinimide does. It is often possible to oxidize only one of several OH groups that may be present in a molecule. Kinetics of iodination of ketones by N-iodosuccinimide in acetic acid medium was investigated. N-bromosuccinimide has been extensively used both in bromination and in oxidation of many classes of organic compounds. N-bromosuccinimide has been used as the oxidizing agent for the conversion of hydroxylic groups in steroidal alcohols to the corresponding ketones\textsuperscript{73-76}.

Barakat \textit{et al.} used N-bromosuccinimide to oxidize primary and secondary aliphatic alcohols\textsuperscript{76}, aromatic keto-alcohols and secondary alcohols\textsuperscript{77} to the corresponding carbonyl compounds.

Kinetic studies on the oxidation of aliphatic ketones\textsuperscript{78, 79}, cyclic ketones\textsuperscript{80-83} and aromatic ketones\textsuperscript{84,85} by N-bromosuccinimide have been investigated in perchloric acid medium in the presence of mercuric acetate.
Mushran et al.\textsuperscript{86} have investigated the mechanism of oxidation of cyclohexanone by N-bromosuccinimide in the presence of mercuric acetate.

Gopalakrishnan and John Hogg\textsuperscript{87} investigated the kinetics of N-bromosuccinimide oxidation of glycine, alanine and valine as a function of pH.

Corey and Kim\textsuperscript{88} studied the direct and specific methods for the conversion of benzylic and allylic alcohols to alkyl halides by N-bromosuccinimide.

Kinetics of oxidation of benzyl ethers\textsuperscript{89}, \textit{p}-bromophenyl benzyl ether\textsuperscript{90}, substituted benzyl methyl ethers\textsuperscript{91}, cyclic benzyl ether and acetals by N-bromosuccinimide were investigated.

N-bromosuccinimide oxidizes acetals to aromatic esters. Thus benzaldehyde di-ethylacetal is oxidized to ethyl benzoate\textsuperscript{92}.

\[ \text{OR} \quad \text{NBS} \quad \text{Sunlight} \quad \text{OR} \quad + \quad \text{RBr} \]

\textit{p}-nitrobenzaldehyde di-methylacetal on treatment with N-bromosuccinimide gave methyl \textit{p}-nitrobenzoate\textsuperscript{93}. Dialkyl acetals of \textalpha\text{-keto aldehydes are converted to \textalpha\text{-keto esters. For example, pyruvaldehyde diethyl acetal gave ethylpyruvate\textsuperscript{94}.}
Cyclic acetics on treatment with N-bromosuccinimide in CCl₄ gave brominated esters⁹⁵,⁹⁶.

Mathiyalagan and Arulraj⁹⁷ investigated the kinetics and mechanism of oxidation of aromatic acetics with N-bromosuccinimide in acetonitrile medium. Morpholine is a typical compound which belongs to the heterocyclic amines, with oxygen as a hetero atom. The molecular formula is C₄H₉NO and its IUPAC name is tetrahydro-1,4-oxazine. The structure of morpholine is shown below:

![Structure of Morpholine](image)

The reaction of N-chloromorpholine with amines was studied by Ronald and William⁹⁸. They reported the action of N-chloromorpholine on aniline to give azobenzene.
Studies by Pierson and Heamann\textsuperscript{99} on the reaction of N-chloromorpholine with \textit{p}-toluidine seemed to show the formation of 4,4-azotoluene.

Slosson\textsuperscript{100} studied the reaction of N-chloromorpholine with potassium cyanide. He reported that a colourless oily product, N-cyanomorpholine was obtained. Philip and William\textsuperscript{101} studied the reaction of N-bromomorpholine with benzalacetophenone to give a new diastereoisomeric form of \textit{\alpha}-bromo-\textit{\beta}-morpholino benzylacetophenone.

Raymond and Southwick\textsuperscript{102} studied the stereochemistry of the addition reaction of morpholine and N-bromomorpholine to cis and trans \textit{\alpha},\textit{\beta}-unsaturated ketone.
Harpp and Smith\textsuperscript{103} studied the halogenation of acylchlorides. They have reported that acylhalides could be $\alpha$-brominated by the use of N-bromomorpholine and hydrogen bromide.

Reactions of Lewis acids on acetals have passed through the carbocation intermediate\textsuperscript{27,28,44}. The formation of a stable aryl-alkoxy carbocation has been reported by Robinovitz and Bruck\textsuperscript{104} who studied the action of borontrifluoride etherate on aromatic acetals in CDCl$_3$.

Henbest\textsuperscript{105} studied the reaction of some epoxy steroids with the borontrifluoride etherate and established carbocation as the intermediate.
Masaki\textsuperscript{106} investigated the back bone rearrangement of 5α,10α-epoxyalnusan-3β-ylacetate to multiflora 5,8-dien-3β-ylacetate effected by borontrifluoride etherate and the epoxide ring was found to be cleaved to yield a carbocation.

Recently Alphonse\textsuperscript{107} has investigated the action of various Lewis acids on aromatic acetals and proposed mechanism based on carbocation intermediate.

Electrophilic substitution of chlorine in cyclohexanone has been effected by sulphuryl chloride, initiated by the chlorine atom of sulphuryl chloride being coordinated by the oxygen atom of the ether\textsuperscript{108}.

Acetals have undergone oxidative C-O bond cleavage and simultaneous bromination with N,N-dibromobenzene sulphonamide to result in aromatic ester and alkylbromide or brominated esters\textsuperscript{109}.

Esters have been produced\textsuperscript{110} on oxidation of ethers by permanganate. Bromate oxidizes the methine carbon atom of ether into a carbonyl carbon\textsuperscript{111}.
Where,

\( R^1 = \text{alkyl, aryl} \)

\( R^2 = \text{H, alkyl, aryl} \)

\( R^3 = \text{alkyl, (CH}_3)_3\text{Si, t-C}_4\text{H}_9\text{Si(CH}_3)_2 \)