PEROXOVANADATE(V) MEDIATED SYNTHESIS OF QUATERNARY AMMONIUM TRIBROMIDES AND OXIDATIVE ORGANIC BROMINATIONS, SYNTHESIS AND STRUCTURAL ASSESSMENT OF NEWER HETEROLIGAND DIPEROXOVANADATES(V) AND EFFICACY OF A NEW CHROMIUM(VI) REAGENT

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by

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CERTIFICATE

It is certified that the work contained in the thesis entitled "PEROXOVANADATE(V) MEDIATED SYNTHESIS OF QUATERNARY AMMONIUM TRIBROMIDES AND OXIDATIVE ORGANIC BROMINATIONS, SYNTHESIS AND STRUCTURAL ASSESSMENT OF NEWER HETEROLIGAND DIPEROXOVANADATES(V) AND EFFICACY OF A NEW CHROMIUM(VI) REAGENT" by Upasana Bora, a student in the Department of Chemistry, Indian Institute of Technology, Guwahati for the award of degree of Doctor of Philosophy has been carried out under my supervision and that this work has not been submitted elsewhere for a degree.

12 July, 2002. **Mihir K. Chaudhuri**

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CERTIFICATE

This is to certify that Ms. Upasana Bora has satisfactorily completed all the courses required for the Ph.D degree programme.

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CHM 601	Physical Methods in Chemistry
CHM 610	Organometallics
CHM 620	Art in Organic Synthesis
CHM 621	Newer Reagents in Organic Synthesis

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Dedicated

to my

beloved Ma

Acknowledgement

I thank my supervisor, Professor Mihir K. Chaudhuri for the lessons that he taught me. He taught me chemistry and …much more. He taught me how to seek perfection and he also taught me the importance of a disciplined mind.

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I thank my father for the lessons that he taught me when I was a child, and…for his blessings, which are always with me.

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I thank my sister, brother-in-law and Nicky for the way they make me feel so special and important.

And, I thank God for being there for me in a way no one else can.

(Upasana Bora)

CONTENTS

ABSTRACT

The thesis of afore mentioned title is based on the results of a few chosen aspects of peroxovanadium(V) and oxofluorochromium(VI) chemistries. While it focuses, in part, on peroxovanadate(V) mediated synthesis of quaternary ammonium tribromides and oxidative organic brominations, a relatively smaller section of the text is dedicated to the synthesis and structural assessment of a set of newer heteroligand diperoxovanadates(V). The other part of the thesis manifests the efficacy of a new chromium(VI) reagent, especially for Δ^5-steroidal oxidations. The subject matter is spread over five chapters:

Chapter 1: *Introduction and scope of the work*

Chapter 2: *Methods of preparation of starting materials, elemental analyses and the details of instrumental techniques used for characterization and structural assessment of the compounds*

Chapter 3: *Peroxometal mediated environmentally favorable route to brominating agents and protocols for bromination of organics*

This Chapter is divided into two parts A and B.

Part A: *Quaternary ammonium tribromides (QATBs) [QA = tetramethylammonium (TMA), tetraethylammonium (TEA), tetrabutylammonium (TBA) and cetyltrimethylammonium (CTMA); TB = Br_3^-] : Clean synthesis, characterization and efficacy of QATBs as brominating agents*

Part B: Regioselective bromination of organic substrates by tetrabutylammonium bromide promoted by V_2O_5—H_2O_2: An environmentally favorable synthetic protocol

Chapter 4: *Synthesis and structural assessment of diperoxovanadate(V) complexes containing 3,5-dimethylpyrazole as the heteroligand*

Chapter 5: *Oxidation of selected organic substrates using a new reagent, 3,5-dimethylpyrazolium fluorochromate(VI), $C_5H_8N_2H[CrO_3F]$, **DmpzHFC***

Each chapter is a self-contained one, having also a bibliography at the end containing the appropriate references as cited in the text. An outline of the content of each chapter is given below:

Chapter 1: Introduction and scope of the work

Introduction to the thesis presents an overview of the different aspects of peroxovanadium(V) and oxofluorochromium(VI) chemistries. It discusses in brief a rather long, complicated but gifted background of peroxovanadium(V) chemistry thus bringing out its direct relevance to applied aspects of commercial importance and biochemical relevance in addition to connecting the results of laboratory experiments with the so far understood biochemistry of the vanadium bromoperoxidase (VBrPO) enzyme. In this chapter is also highlighted the anticipated contribution of this chemistry in the development of newer as well as environmentally safer routes to quaternary ammonium tribromides, underscoring the importance of these compounds as key reagents in bromination chemistry. It has been emphasized while dwelling on the chemistry of peroxo-vanadium(V) that the burgeoning knowledge of activity of the natural vanadium(V) enzyme VBrPO might provide cues leading to the development of new and relatively cleaner protocols for bromination.

That the search for targeted new heteroligand peroxovanadates(V) is still on the upstream of the collective endeavour in this area has been duly acknowledged implying in the process the importance of synthesis of diperoxovanadates(V) having appropriate heteroligands. What is anticipated is that with the successful synthesis of such type of compounds, one might eventually be able to come forward with a new and highly potent insulin mimic.

In yet another manifestation of the reaction chemistry of transition metals, the oxidation chemistry of oxochromium(VI), with special reference to fluorochromate(VI), is brought forward for a brief discussion. Emerged thereof is, therefore, a common link between the two parts of the total text of the thesis, and that addresses the treasure of transition metal assisted oxidation chemistry. This section while presenting a non-exhaustive account of the chromium(VI) reagents, that are in existence, emphasizes the fact that the search for better performing oxidizing reagents still continues.

A critical account of topical importance of the chosen problems in Chemical Sciences scenario leads to a wide and rewarding scope of the work being embodied in the thesis and much more beyond.

Chapter 2: Methods of preparation of starting materials, elemental analyses and the details of instrumental techniques used for characterization and structural assessment of the compounds

In order to prove the authenticity of any chemical synthesis, chemical analysis and instrumental studies are imperative. **Chapter 2** of the thesis elaborates

on the chemical procedures that are followed and the instrumental descriptions of those used.

Chapter 3: Peroxo-metal mediated environmentally favorable route to brominating agents and protocols for bromination of organics

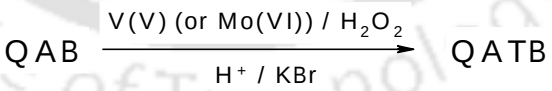
While working on the reactivity of peroxometal compounds, especially oxidation of halides, attention was drawn to the development of newer and ecofriendly brominating agents and bromination protocols. These are sought after because of the use of brominated organic molecules as precursors for the preparation of pharmaceuticals, agrochemicals, speciality chemicals and so on.

The bromoorganics, particularly bromoaromatics, are generally prepared involving toxic chemicals, for instance, Br_2 which has been a cause of great concern globally. Keeping environmental safety in sight, one would like to by-pass routes involving such chemicals, without sacrificing the goal of obtaining the target molecules with acceptable yield and cost. Indeed, it has been possible to develop newer and ecofriendly brominating agents and bromination protocols as has been elaborated in **Chapter 3**. In order to make the presentation more articulate, the Chapter has been divided into two parts. **Part A** of **Chapter 3** includes the synthesis of a series of quaternary ammonium tribromides followed by their characterization and a few demonstrative examples in favour of their efficacies as brominating agents, while the methodology for oxidative organic brominations, without isolating the active brominating species, is incorporated in **Part B** of **Chapter 3**.

Part A: Quaternary ammonium tribromides (QATBs) [QA = tetramethyl-ammonium (TMA), tetraethylammonium (TEA), tetrabutylammonium (TBA) and cetyltrimethylammonium (CTMA); TB

= Br_3^-] : Clean synthesis, characterization and efficacy of QATBs as brominating agents

After the initial success in the synthesis of tetrabutylammonium tribromide, **TBATB,** $(C_4H_9)_4NBr_3$, it became necessary to make value additions to the process of synthesis because it was hoped to be one of the reagents of choice for organic brominations and might as well be commercially viable. This led to a set of experiments summarized as the optimization of preparation protocol of **TBATB**. The details of these experiments are laid out in this chapter. In order to demonstrate the scope of the philosophy of peroxovanadate(V) mediated synthesis of quaternary ammonium tribromides, the reaction strategy being used for synthesis of TBATB was applied to three other cases by changing the bromide source from TBAB to TMAB through CTMAB and TEAB. This chapter also discusses the successful synthesis of tetramethylammonium tribromide, **TMATB,** $(CH_3)_4NBr_3$, tetraethyl-ammonium tribromide, **TEATB,** $(C_2H_5)_4NBr_3$, and cetyltrimethylammonium tribromide, **CTMATB,** $(C_{16}H_{33})(CH_3)_3NBr_3$. (Scheme 1)

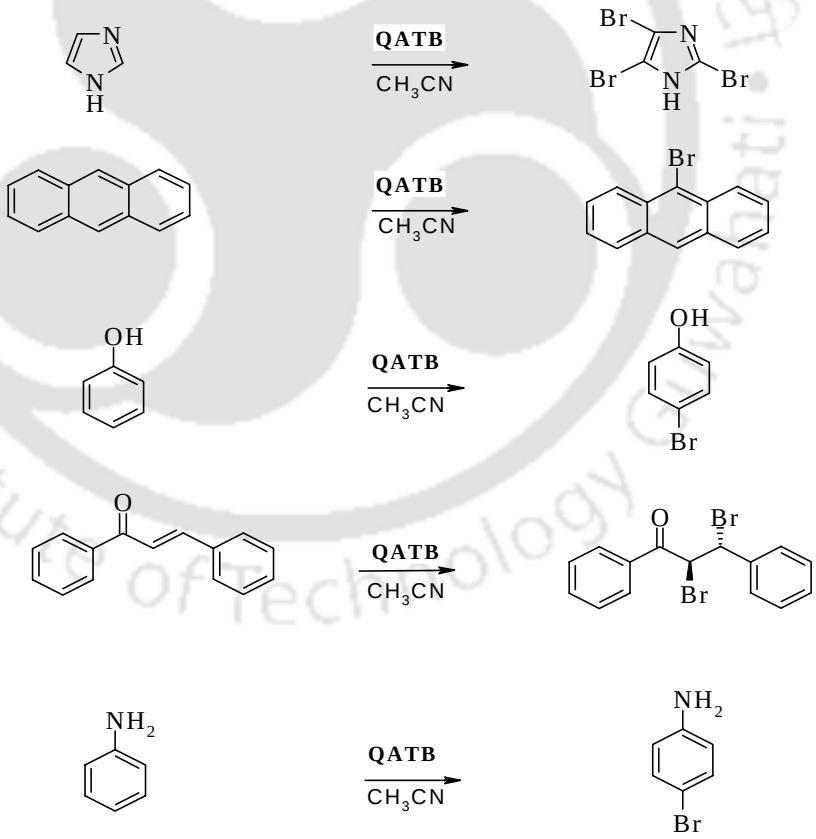


QAB = quaternary ammonium bromide
QA = quaternary ammonium, *viz.*,
tetramethylammonium
tetraethylammonium
tetrabutylammonium
cetyltrimethylammonium
QATB = quaternary ammonium tribromide

Scheme 1

The chemical synthesis of any compound is always followed by its characterization by physicochemical methods. The above-mentioned compounds were characterized by different spectroscopic techniques in addition to chemical analyses and solution electrical conductance measurements.

In order to probe the versatility of QATBs as brominating agents, a few selected reactions were conducted using acetonitrile as the solvent. Scheme 2 is a graphical representation of some of the bromination reactions that were carried out to test efficacy of the brominating agents.



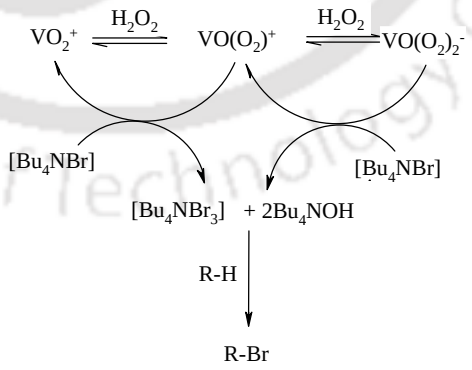
Scheme 2

Part B: Regioselective bromination of organic substrates by tetrabutylammonium bromide promoted by V_2O_5-H_2O_2: an environmentally favorable synthetic protocol

In **Part B** of **Chapter 3** is presented the details of a methodology for the regioselective bromination of organic substrates by tetrabutylammonium bromide promoted by V_2O_5-H_2O_2 in an environmentally benign way.

The strategy was based on the activation of dioxygen through the interaction of H_2O_2 with V(V) leading to the peroxovanadium(V) species (λ = 430 nm) in solution followed by the oxidation of Br^- by the peroxovanadium(V) intermediate (λ = 267 nm) as the active brominating agent, and finally bromination of organic substrates to afford bromoorganics. (Scheme 3)

The reactions were conducted at *ca.* 5 °C in an acetonitrile/water solvent system using an optimized stoichiometry of the reagents to afford the desired products in high to very high yields.

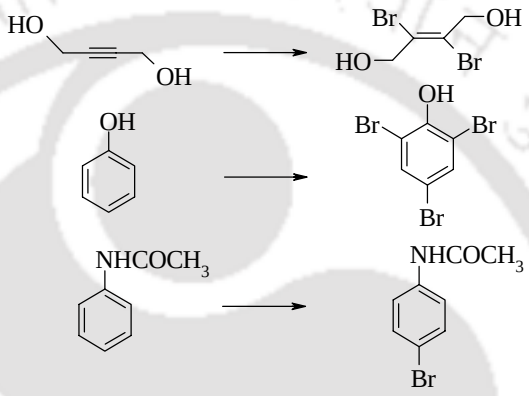


Scheme 3

It appears that sufficient acid could be generated in the process from the use of 0.5 molar equiv of V_2O_5 to allow for bromide oxidation by the peroxovanadium(V)

species that formed in the reaction. The methodology is capable of being made catalytic with KBr as the consumable source of bromide.

This methodology allowed bromination of a series of substrates, of which some have been graphically represented below, in Scheme 4:

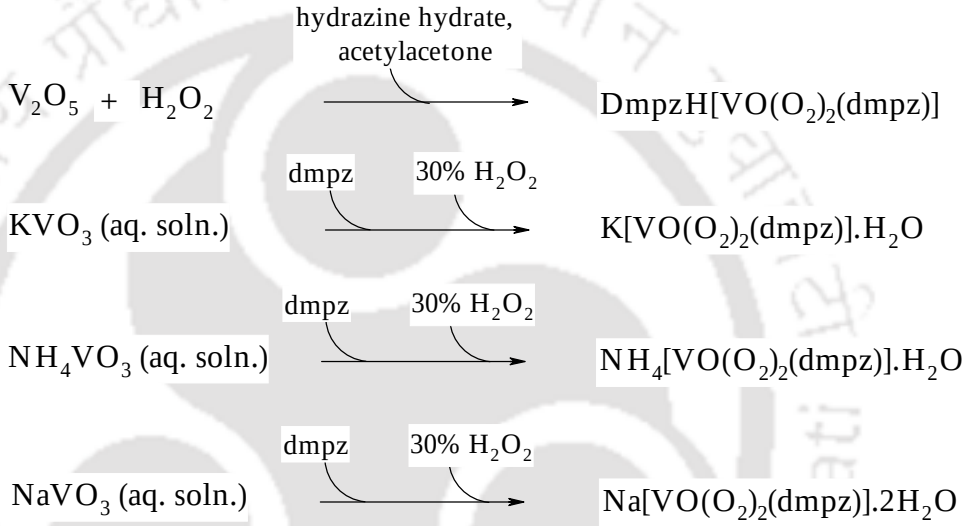


Scheme 4

Chapter 4: Synthesis and structural assessment of diperoxovanadate(V) complexes containing 3,5-dimethylpyrazole as the heteroligand

While exploring the reaction profiles of peroxovanadium(V) complexes, the importance of synthesis of peroxo and heteroligand peroxovanadates cannot be underestimated. The reason for this can be accredited to the potential of these complexes to act as models for understanding biologically important molecules, besides being shown to be capable of oxidizing organic substrates. Diperoxovanadium(V) species have assumed a great timely important relevance owing to their potential as clinical alternatives of insulin for the treatment of diabetes and there has been an immense interest in the design of suitably ligated water soluble diperoxovanadates(V), that can mimic the insulin activity, and continuing work by

several groups including ours has resulted in the synthesis of a few such complexes. As a part of a programme of our laboratory, we have now succeeded to gain an access to $[VO(O_2)_2dmpz]^-$, (Scheme 5), though we had earlier failed to synthesize the corresponding imidazole derivative.



Scheme 5

An interest in the design and development of such heteroligand peroxovanadate(V) complexes is also owing to their amenability to electronic spectroscopic studies. The study of electronic structures of the metal-dioxygen unit is of interest in relation to bonding of O_2 to the metal centers in metalloenzymes, oxygen-carrying proteins, and also to catalytic oxidations.

An attempt to X-ray delineation of structure of the afore-mentioned compounds has not led us much ahead owing to instability of the compounds. However, some essential points of similarities, between $[VO_2F(dmpz)_2]$ and $[VO(O_2)_2(dmpz)]^-$ in terms of the oxidation state of the metal and similarities in

vibrational spectral pattern in respect of the metal-dmpz ligand interactions cause us to believe that the basic structural motif, in so far as the 3,5-dimethylpyrazole to metal bonding is concerned, is similar. Figure 1 is the ORTEP diagram of $[VO_2F(dmpz)_2]$.

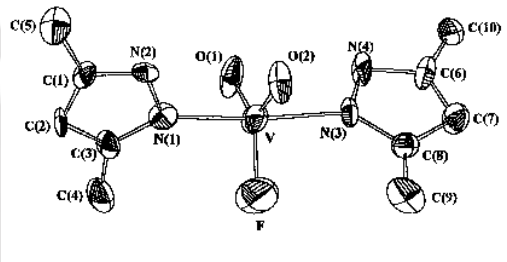


Figure 1

Chapter 4 thus reports the successful synthesis of a set of four heteroligand diperoxovanadium(V) complexes having 3,5-dimethyl pyrazole as the heteroligand. Characterization of the complexes was made on the basis of elemental analyses and a variety of spectroscopic studies and it would not be out of place to mention that the compounds reported in this chapter exhibit a rather typical electronic spectral pattern and may provide an excellent scope for study of the peroxo-metal interactions in solution.

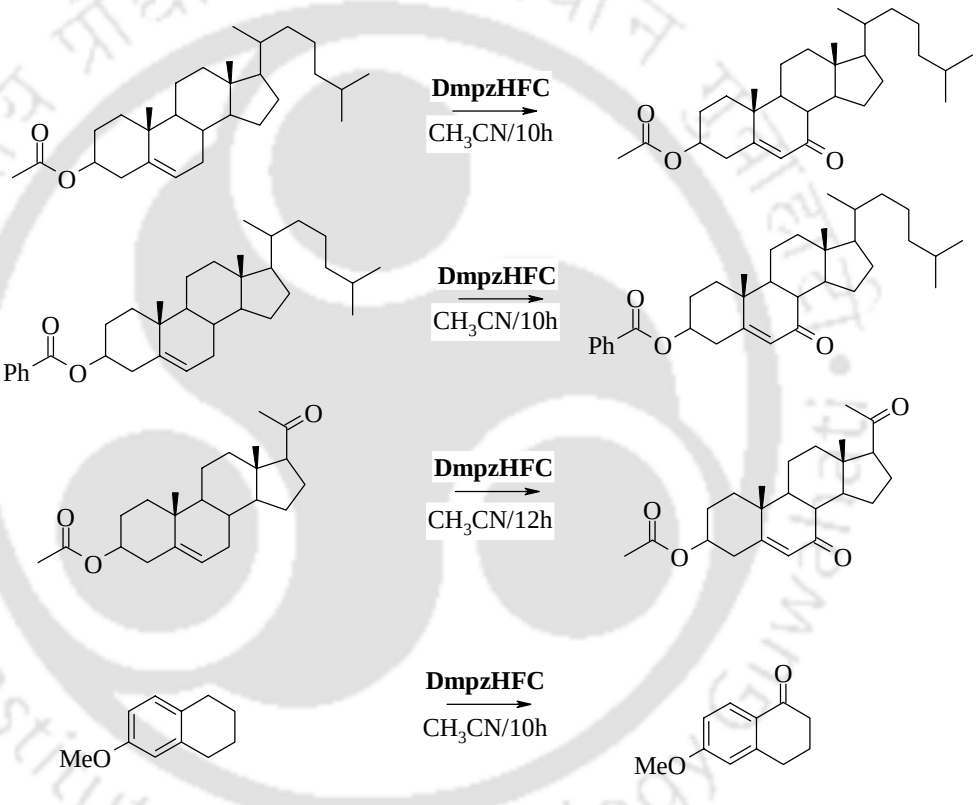
Chapter 5: Oxidation of selected organic substrates using a new reagent, 3,5-dimethylpyrazolium fluorochromate(VI), DmpzHFC, $C_5H_8N_2H[CrO_3F]$

Quite apart from what has been discussed above, partial oxidations of organic substrates have always been commercially very important and for this purpose no other reagent could be as popular, as useful and as successful as the chromium (VI)

reagents have been. Though there are some limitations of chromium reagents in terms of environmental antagonism (a problem which can be solved, however, by a careful disposal of the chromium waste by trapping in a solid bed), the popularity of such reagents does not seem to diminish because their performance under mild conditions with high efficiency and cost-effectiveness weigh far over their limitations.

Over the years, a host of chromium (VI) reagents have been developed for such transformations with oxidants like pyridinium chlorochromate (**PCC**), pyridinium fluorochromate (**PFC**) and pyridinium dichromate (**PDC**) being in regular use. While these reagents are no doubt very versatile, however, when it came to the oxidations of some selected substrates, they reacted rather sluggishly. The selected substrates referred to above have been drawn from Δ^5-steroids, because Δ^5-steroids with a keto functionality at the 7-position are much sought after owing to their medicinal values as reported in literature. 6-Methoxy tetralone is another substrate that has importance in some medicinal preparations. And this problem caught our attention at a juncture when a new chromium(VI) reagent, 3,5-dimethylpyrazolium fluorochromate(VI), **DmpzHFC**, $C_5H_8N_2H[CrO_3F]$, was just developed in our laboratory as a companion of **PFC** but with a few improved properties. What was observed was that **DmpzHFC** possesses all the good qualities that **PFC** has, and the results of a few preliminary reactions indicated that the new reagent might work better in situations where **PFC**, **PCC** or similar reagents reacted sluggish.

Thus, on applying the reagent to the oxidation of Δ^5-steroids, it has now been demonstrated that a lesser amount of reagent afforded the desired products in considerably good yields in a comparatively shorter time, as has been graphically presented in Scheme 6.



Scheme 6

Chapter 5, indeed the concluding the chapter of the thesis, presents all the results of our studies related to 3,5-dimethyl pyrazolium fluorochromate(VI), **DmpzHFC,** oxidations.

LIST OF FIGURES

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

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INTRODUCTION AND SCOPE OF WORK

Chapter 1

With transition-metal-catalyzed oxidation reactions being some of the most fundamental reactions in both inorganic and organic chemistry, there has been for many years now an intrinsic chemical interest in the synthesis, characterization, and reactivity studies of systems amenable to such activity. While oxo-metallates such as the oxo-chromates and permangantates (*c.f.* Mn(VII)) occupy the center-stage as far as partial oxidations are concerned,[1] metal-dioxygen complexes, of which peroxo-metallates take a large share, are another type of complexes that are of interest for their immense use as industrial catalysts[2] and because of their importance in biological systems.[2]

It may be mentioned, while discussing metal-dioxygen chemistry, that although the term molecular oxygen refers only to the free uncombined O_2 molecule with ground state $^3\Sigma_g$, the term dioxygen is used as a generic designation for the O_2 moiety in any of its several forms, and can refer to O_2 in either a free or combined state.[3] Dioxygen binding is subdivided into two main types, superoxide and peroxide and accordingly, the addition of one or two electrons to a neutral O_2 results in formation of the superoxide (O_2^-) and peroxide (O_2^{2-}) species, respectively, leaving the superoxide species with bond order of 1.5 and the peroxide with a bond order of 1; a situation that is best understood in terms of the molecular orbital theory.[4]

Molecular oxygen is a paramagnetic molecule having a triplet $^3\Sigma_g$ ground state as mentioned above and molecular orbital description of the $^3\Sigma_g$ level is

$$O_2\ KK(2s\sigma_g)^2(2s\sigma_u^*)^2(2p\pi_u)^4(2p\pi_g^*)^1(2p\pi_g^*)^1,$$

in which the KK term indicates that the K shells of the two oxygen atoms are filled. The two unpaired electrons in the $^3\Sigma_g$ ground state are found in the two

degenerate antibonding $2p\pi_g^*$ orbitals, leaving O_2 with a formal bond order of two. The molecular orbital description of O_2 ($^3\Sigma_g$) shows a vacancy for the addition of a single electron each in both of the $2p\pi_g^*$ orbitals. (Figure 1.1) Addition of two electrons to these orbitals results in the formation of peroxide. Accordingly, a metal-peroxide complex is one in which the coordinated dioxygen resembles a peroxide (O_2^{2-}) anion.[5] The difference in the reactivity between peroxo and unreduced dioxygen complexes, whether binary or heteroligand, reveals that the chemistry of the two are very different owing to the presence of two extra electrons in the anti-bonding O- $p\pi^*$ orbital of the peroxide ion.

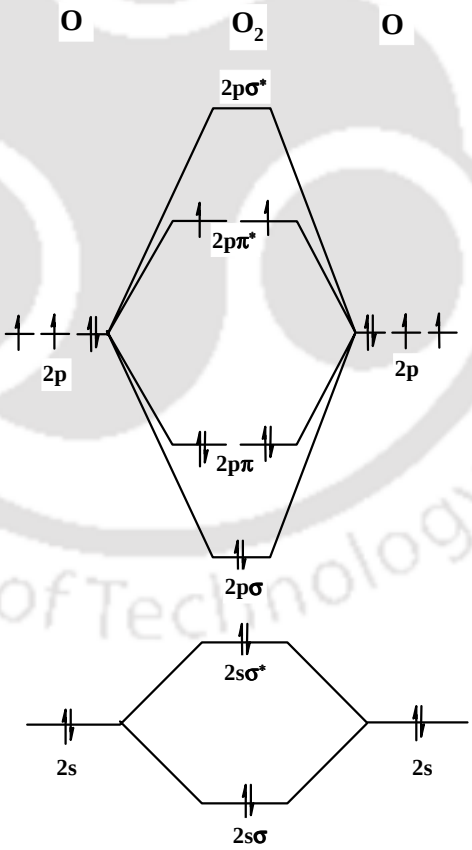
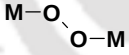
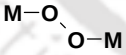


Figure 1.1. Molecular Orbital Diagram for O_2

The modes of bonding of peroxide to metals are quite varied and interesting from the structural viewpoint. It can range from a symmetrical bidentate to a terminal monodentate position including all the possible angles in between. The bridging μ-peroxo could vary from cis-planar and trans-planar to trans-nonplanar configurations. Deviations from ideal symmetry are common and in the cases of heteroligand fields these deviations are, at times, due to the inherent symmetry of different donor atoms. Table 1.1 shows the way in which a peroxo group is expected to coordinate to metals.[6]

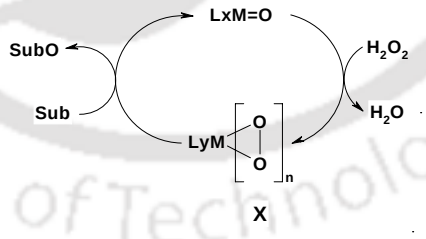
Table 1.1. Structural Classification of Dioxygen Complexes

Structural type	Structural designation	Vaska classification
	η^1 dioxygen	Type a (superoxo)
	η^2 dioxygen	Type II a (peroxo)
	$\eta^1 : \eta^1$ dioxygen	Type I b (superoxo)
	$\eta^1 : \eta^1$ dioxygen	Type II b (peroxo)
	$\eta^2 : \eta^2$ dioxygen	
	$\eta^1 : \eta^2$ dioxygen	

While simple peroxometallates (*c.f.* binary peroxides and peroxo-metals) are often unstable, suitably ligated peroxometal complexes can be isolated and stored in many instances for prolonged periods.[6,7,8] A significant feature of these

complexes is that the O-O bond is relatively weak (120-190 $kJmol^{-1}$)[9] and can be easily cleaved. And depending on their mode of cleavage peroxo complexes can involve in either polar or radical oxidations. If the bond is cleaved heterolytically, polar oxidations will take place whereas if the cleavage is homolytic, radical oxidations will be observed.[10,11] It is rather interesting that often the nature of the heteroligands can dramatically change the reactivity of peroxo complexes so much so that even when the metal is the same the complexes may shift their behaviour from polar to radical oxidants.

Peroxo-transition metal complexes can be obtained either by electron-transfer reactions between a suitably chosen lower valent transition metal and O_2, or by the reaction of transition metals with hydrogen peroxide. They are much sought after as very important oxidants.[12] By nature of reactivity they can be classified either as stoichiometric reagents or as catalytic agents. The general mechanism of catalysis, if the catalyst is not isolated, has been described graphically in Scheme 1.1, in which

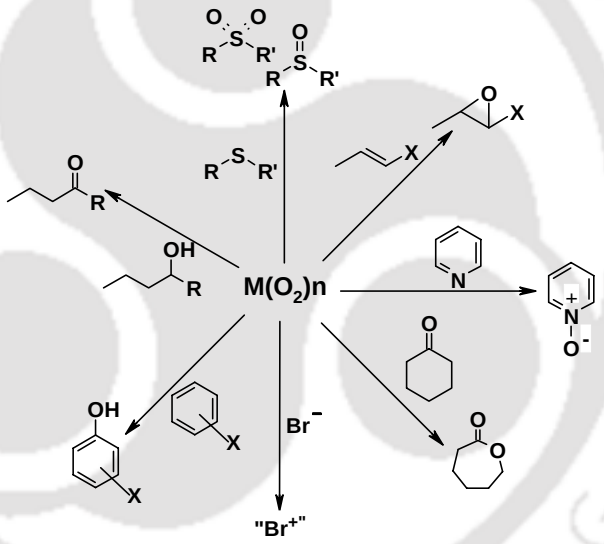


Scheme 1.1. A General Mechanism for Catalytic Oxidation by Peroxo-Transition Metal Complexes

'X' is the real oxidant in solution. Its reduced form adds hydrogen peroxide again thus accounting for the catalysis.[12]

One of the main reasons for the commercial importance of peroxo-metallates lies in the fact that the peroxide (O_2^{2-}) is activated by a higher-valent transition

metal rendering it suitable for effective oxidations. Notable is that though hydrogen peroxide is an oxidant which is also not environmentally demanding, with water being its only by-product,[13] unfortunately it alone is a very weak oxidant in many instances. Thus, in order that the reactions become synthetically significant and commercially viable the oxidations by hydrogen peroxide need to be catalyzed.[14] Among the oldest but very efficient catalysts that have been discovered are the derivatives of some transition metal ions like V, Mo and W in their highest oxidation states.

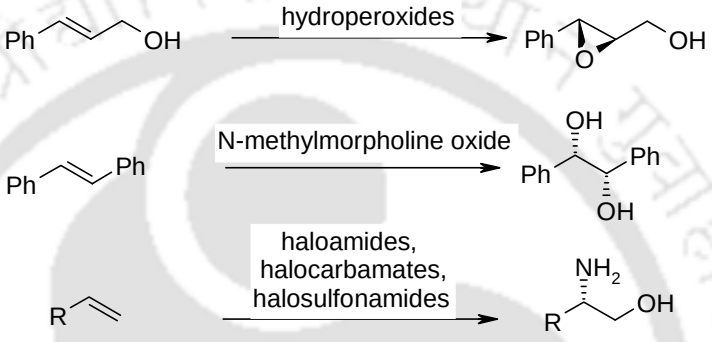


Scheme 1.2. Selected Oxidations of Organic Compounds by Peroxo-Metal Complexes (M = Ti, V, Mo, W)

Yet newer manifestations of their reactivity profiles are still under investigation.[9,15] Needless to mention that the peroxo-metal complexes referred to above are much stronger oxidants than H_2O_2 with their reactivity being many orders of magnitude larger than that of hydrogen peroxide.[9,11,14,16,17] A few examples in Scheme 1.2 show the versatility of peroxometal oxidants.[12]

Highly relevant and significantly important to be known in this context are Sharpless's reagents[18] like hydroperoxides,[19,20] N-methylmorpholine oxide

$K_3[Fe(CN)_6]$,[21,22] haloamides, halocarbamates and halosulfonamides[23,24] for instance, that are extremely important for catalytic assymmetric oxidations such as the asymmetric epoxidation of allylic alcohols (Katsuki-Sharpless epoxidation), [19,20] the asymmetric dihydroxylation of olefins[21,22] and the asymmetric aminohydroxylation of alkenes. [23,24] (Scheme 1.3)



Scheme 1.3. A few Catalytic Asymmetric Oxidations

While there is no doubt that much of the attention drawn by the peroxometal complexes is because of their importance as oxidants, there has also been a great deal of interest this chemistry owing its origin to a scientific compulsion to understand the chemistry of the active sites of biological dioxygen carriers and also the closely related biological dioxygen activators.[25] The unambiguous evidence for the presence of metal-dioxygen units ('M-O_2') in the oxidized forms of some important biological substances like hemoglobin, hemerythrin and hemocyanin, for instance, has rendered the investigations related to their synthetic, structural and reactivity aspects not only very intriguing but also relevant to the understanding of their biochemical implications.

In the domain of peroxometal chemistry, studies involving vanadium have drawn considerable attention of contemporary researchers in recent years. A chronology of the development reveals that earlier (prior to 1980) the attention of

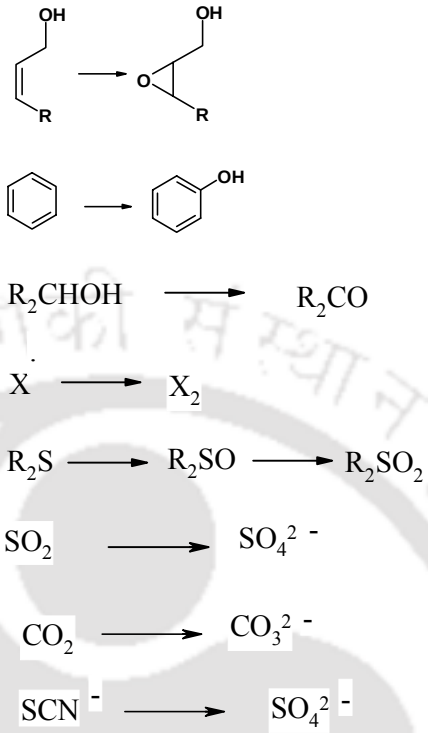
most of the workers of peroxovanadium chemistry was engaged in the studies of solution behaviour of such complexes and ramifications thereof,[26-30] from the early eighties on the importance of isolation in the solid state started gaining recognition and hence further investigations involving them.[31-35] Also gaining importance was the coordination chemistry of vanadium(V) and vanadium(IV) in order to explore the biochemical implications of coordination environment and geometry around the metal centre.[36,37] Then there was an advent of the era of synthesis, structural dilineation, catalysis and biomodelling which has eventually begun to occupy a good portion of the center stage.[38,39] The interest in biomodelling was largely triggered by the discovery[40] of a class of marine enzymes (vanadium bromoperoxidase) requiring vanadium(V) and hydrogen peroxide for their activity, which are responsible for the production of a large variety of halogenated organics.[41] Commercial importance of bromoorganics, especially bromoaromatics,[42,43] as well as an intense interest in understanding the intricate reaction mechanism of these enzymes has caused research in vanadium bromoperoxidase related chemistry to be a major thrust area in many chemical laboratories.[44,45] Yet another manifestation of peroxovanadium chemistry is the potential of complex peroxovanadium species as a clinical alternative of insulin for the treatment of diabetes.[46-48] This area is also very promising and is currently receiving a lot of attention.[38,49] Some more discussion will be made on this aspect later in this Chapter.

The group with which the present Ph.D research has been carried out has been involved in the synthesis and structural assessment of inorganic compounds, followed by looking into their reaction profiles with an intent to understand the

underlying intricacies concerning their catalytic and biochemical activities. Peroxometal chemistry is one area that has received a lot of attention of our research group and the peroxometals have so far been drawn mainly from Ti,[50-53] V,[54-62] Mo, W, Zr,[63] Th[64] and UO_2^{2+}. [56, 65-71] Among these, it is vanadium that seems to have claimed the biggest share and a large number of peroxo and heteroligand peroxovanadates(V) were synthesized in our laboratories. Subsequently (1985 on), the reaction chemistry of peroxovanadates(V) became one of the thrust areas of our investigations.[72-82] Indeed it is at these manifestations of peroxovanadium chemistry where the present Ph.D research found its root.

Interestingly, peroxovanadium chemistry is very flamboyant and by varying the pH values or in other words by changing the pH of the reaction solutions, different species of the type $[VO(O_2)]^+$, $[VO(O_2)_2]^-$, $[VO(O_2)_2(H_2O)]^-$, $[VO_2(O_2)_2]^{3-}$ $[VO(O_2)_3]^{3-}$, $[V(O_2)_3]^-$ and $[V(O_2)_4]^{3-}$, [83, 57] for example, are formed and the number of peroxo groups coordinated to a vanadium center generally increases with an increase in pH or alkalinity of the reaction solution.

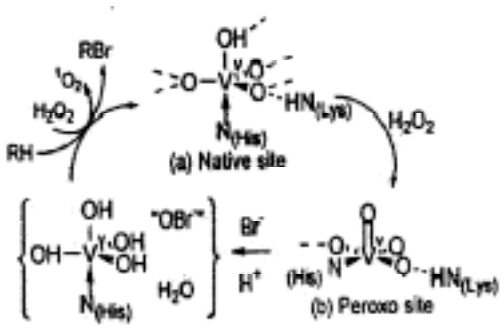
In so far as the reactivity is concerned, peroxovanadium(V) complexes are recognized as selective oxygen transfer species, which can bring about a wide range of two-electron oxidation reactions.[84] The complexes have the ability to oxidize both organic and inorganic substrates, allowing facile alkene epoxidations and hydroxylations of aromatics, alkane and alcohol oxidations, halide, sulfide, sulphur dioxide, carbon dioxide and thiocyanate oxidations to be possible, as summarized in Scheme 1.4.[73,74,79,84]



Scheme 1.4. Examples of the Reaction Types Mediated by Peroxovanadium(V) Complexes

The involvement of peroxovanadates as catalysts in living systems was realized in 1983-84 when Vilter *et al.* reported the discovery of the vanadium bromoperoxidase (VBrPO)[40] enzyme from the marine algae *Ascophyllum nosodum*. The haloperoxidases (of which VBrPO is a member) are a group of enzymes which usually contain the FeHeme moiety or vanadium as an essential constituent at their active site, though a few haloperoxidases which lack a metal cofactor are also known.

Vanadium haloperoxidases (VHPO) are found in marine algae, lichens and certain terrestrial fungi and are known to catalyze the halogenations — chlorination, bromination and iodination — of organic substrates or the halide-assisted disproportionation of hydrogen peroxide (Scheme1.5).



Scheme 1.5. Proposed Catalytic Cycle for VHPO

The X-ray structures of vanadium haloperoxidases (VHPOs) are expected to serve as 'blueprints' not only to provide cues for the construction of low molecular weight analogous and mimics but also to give information about the active site composition and geometry. The present status, in so far as VHPO is concerned, is the following.[45] The X-ray structures of VClPO from *Curvularia inaequalis* and the vanadium bromoperoxidases (VBrPO) from *Corallina officinalis* and *Ascophyllum nosodum* reveal that the active site resembles vanadate (HVO_4^{2-}) which is coordinated to the protein by one histidine residue in a trigonal bipyramidal geometry (Scheme 1.5). The histidine that directly binds vanadium(V) and the amino acids involved in H-bonding to the vanadate oxygen atoms are conserved. Further, structural characterization of VClPO from *C. inaequalis* in the presence of H_2O_2 shows that the metal (V(V)) is coordinated axially by a terminal oxo group, and equatorially by peroxide, histidine, and the oxide ligand, in square pyramidal geometry (Scheme 1.5). Clearly in the enzyme the peroxo ligand is coordinated to the vanadium(V) centre in an η^2-fashion, in a manner similar to mononuclear vanadium monoperoxo complexes.[84] It is relevant to note that H-bonding seems to be very important in the regulation of metal ion reactivity[85] in biology. Especially important is its effect on the heterolytic

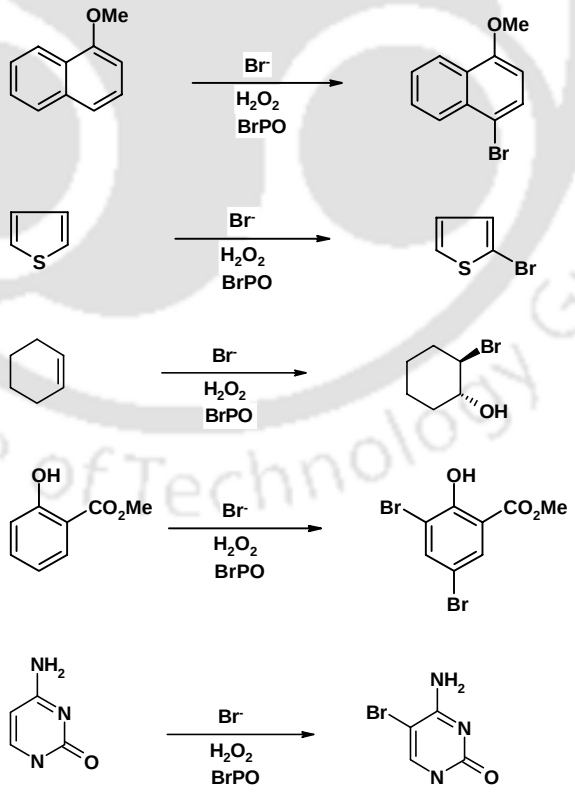
cleavage of O-O bonds in heme enzymes *viz.*, peroxidase and catalase.[85] In view of this, a striking feature at the active site of VClPO is the apparent H-bonding (2.76 Å) between Lys_{353} and the bound peroxide. Albeit peroxo derivatives of VBrPO have not yet been structurally characterized, the conserved amino acid residues found in the active sites of VBrPOs (*C. officinalis and A. nosodum*) suggest that the redundant Lys residues (Lys_{398} and Lys_{349}, respectively) are also appropriately positioned to H-bond to a vanadium(V) — peroxo moiety in VBrPOs.

Moreover, a very important implication of the H-bonding issue discussed above is the outcome of the mechanistic studies of VHPO and its model complexes. Indeed, the results of mechanistic studies of VHPO and VHPO model complexes suggest that peroxide activation may be best achieved by protonation of the V(V) —bound peroxo group to generate a side-on bound hydroperoxide complex.[86] It is believed that an increase in positive charge on a peroxo-oxygen (O_{peroxo}), by protonation, makes attack by halide more favourable.[87,88] As a matter of fact it has been observed in several independent experiments conducted in our laboratories that peroxo-metal mediated bromide oxidation to tribromide (Br_3^-) can be only possible in an appropriately acidic medium.

It is noteworthy that in order to explore the effects that H-bonding from Lys may have on peroxide activation, Butler and co-workers have designed the ligand N-(2-pyridylmethyl-6-amino) iminodiacetic acid, $H_2{}^{NH_2}pyg_2$, with pendant NH_2 functionality, synthesized the heteroligand V(V) complex, $K[VO(O_2)(^{NH_2}pyg_2)]$ and $K[VO(O_2)(^{BrNH_2}pyg_2)]$, and made structural characterization of these complexes as "the first structural characterization of VBrPO model complexes" [45]

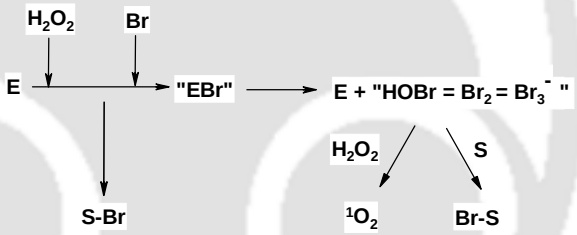
demonstrating direct intramolecular H-bonding between an amine functionality and vanadium(V)-bound peroxide. The distance between NH_2 proton and bound peroxo moiety {(d(N(1) —H···O) : 2.637(4) Å in $K[VO(O_2)(^{NH_2}pyg_2)]$, and 2.640(8) and 2.6919(8) Å in $K[VO(O_2)(^{BrNH_2}pyg_2)]$} are indicative of intramolecular H-bonding. Their results of ^1H NMR studies also revealed that H-bond interaction is significant in solution as well as with the estimated intramolecular H-bond strength in $[VO(O_2)(^{BrNH_2}pyg_2)]^-$ being 6 kcal/mol.

The bromoperoxidase (BrPO) enzyme on coordination with peroxide can oxidize halides, as well as sulfides and pseudohalides and according to literature they are among some of the most efficient oxidants of halides among all the vanadium catalysts so far investigated[44] (Scheme 1.6).



Scheme 1.6. Examples of Vanadium Bromo-peroxidase Catalysed Bromination Reactions

Mechanisms have been proposed by different groups of workers in order to explain the vanadium bromoperoxidase catalyzed bromination reactions. [44,89-93] While it is understood that the reaction proceeds through an oxidized halogen intermediate that is two-electrons above the halide oxidation state, the exact mechanistic pathway is still not known. However, spectroscopic evidence reveals that it is the equivalent of hypobromous acid, bromine, tribromide, or an enzyme-bound bromonium ion-type species that can halogenate appropriate organic substrates (or react with another equivalent of hydrogen peroxide, forming dioxygen). This has been illustrated in Scheme 1.7.[94]



Scheme 1.7. Reaction Scheme Showing Substrate Binding to VBrPO

Due to the problems experienced in using conventional spectroscopic techniques in the analysis of the active center of the VBrPO enzyme, there is a search for simple systems, i.e., low molecular weight analogues that have the ability to mimic the activity of such enzymes.

Importantly in peroxovanadium catalyzed bromide oxidation, vanadium remains in its pentavalent state throughout just as it happens in the enzyme.[95] With this understanding being the basis, a number of oxo-peroxo complexes of vanadium(V) have been subsequently synthesized in quest of functional models for vanadium-haloperoxidases[45,95] The development that we regarded to be the

latest to our knowledge till the time this section of the present thesis was written is the contribution of Butler and her co-workers[45] as already highlighted earlier in the Chapter.

VO_2^+ is regarded as a functional mimic of VBrPO although, unlike VBrPO, it functions in acid and at much lower turnover rates.[93] *Cis*-dioxovanadium(V) in acidic solution coordinates 1 or 2 equiv of hydrogen peroxide forming the red monoperoxo, $VO(O_2)^+$, or the yellow diperoxo, $VO(O_2)_2^-$ species, as described by the following equations

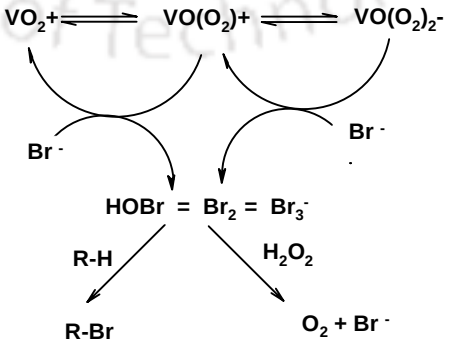
$$VO_2^+ + H_2O_2 \leftrightarrows \underset{\text{(red)}}{VO(O_2)^+} + H_2O$$

$$VO(O_2)^+ + H_2O_2 \leftrightarrows \underset{\text{(yellow)}}{VO(O_2)_2^-} + 2H^+$$

and it is believed[96] that under more acidic conditions (pH $\leq$ 2), dioxotriperoxodivanadium(V), $(VO)_2(O_2)_3$, forms from the dimerization of $VO(O_2)^+$ and $VO(O_2)_2^-$:

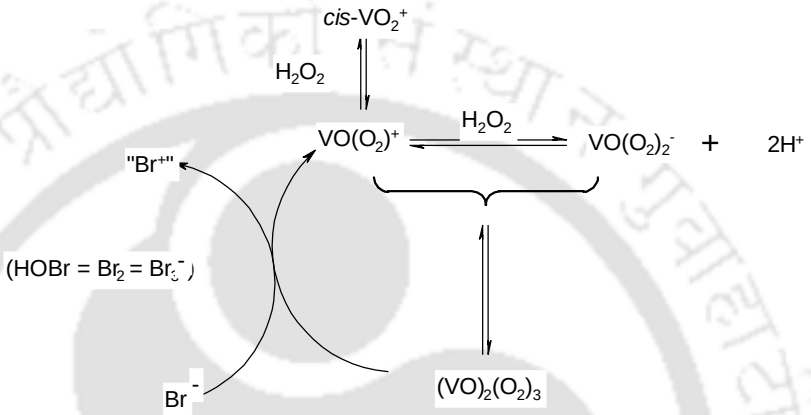
$$VO(O_2)^+ + VO(O_2)_2^- \leftrightarrows (VO)_2(O_2)_3$$

Though both monoperoxo and diperoxo vanadium(V) species are capable of bromide oxidation and hydrogen peroxide disproportionation (Scheme 1.8),[84]



Scheme 1.8. VO_2^+-Catalyzed Oxidation of Bromide by Hydrogen Peroxide

kinetic and spectroscopic evidences cause certain schools of thought to believe that it is the triperoxovanadium(V) complex, $(VO)_2(O_2)_3$, that is actually involved in the oxidation of Br^-. [96,97] This has been explained schematically in Scheme 1.9. However, this perception may be regarded as contentious.



Scheme 1.9. Proposed Mechanism of Bromide Oxidation involving a $(VO)_2(O_2)_3$ Intermediate

The afore mentioned discussions are convincing enough to believe that the synthesis of mimics of the naturally occurring vanadium peroxidase enzymes is a very important area of research in itself. Importantly, an understanding of their reactivity profiles provide important cues in the development of bromoperoxidase mimics as greener alternatives to the environmentally noxious brominating agents. But a full appreciation of this relevance requires that the importance of bromination chemistry be fully appreciated.

Naturally occurring organobromines, which range in structural intricacy from the simple but enormously abundant bromoform ($CHBr_3$) and bromomethane to the highly complex bryozoan bromine-containing indole alkaloids, are produced by marine and terrestrial plants, marine animals, bacteria, fungi, some higher animals, and a few mammals including humans. [41-43] Bromoaromatics are

biologically important, as they are believed to be involved in chemical defense roles to keep predators away from a particular organism. Extensive applications of bromoorganics cause bromination chemistry to be a thrust area in many research laboratories. In the chemical industry bromo-compounds are widely used as intermediates in the manufacture of pharmaceuticals, agrochemicals, flame retardants and other speciality chemical products[43] as some of the important activities of bromoorganic compounds include antifungal, antibacterial, antineoplastic, antiviral (e.g., anti-HIV) and anti-inflammatory actions.[41,43] Some examples of the naturally occurring bromoorganics are shown in Figure 1.2.

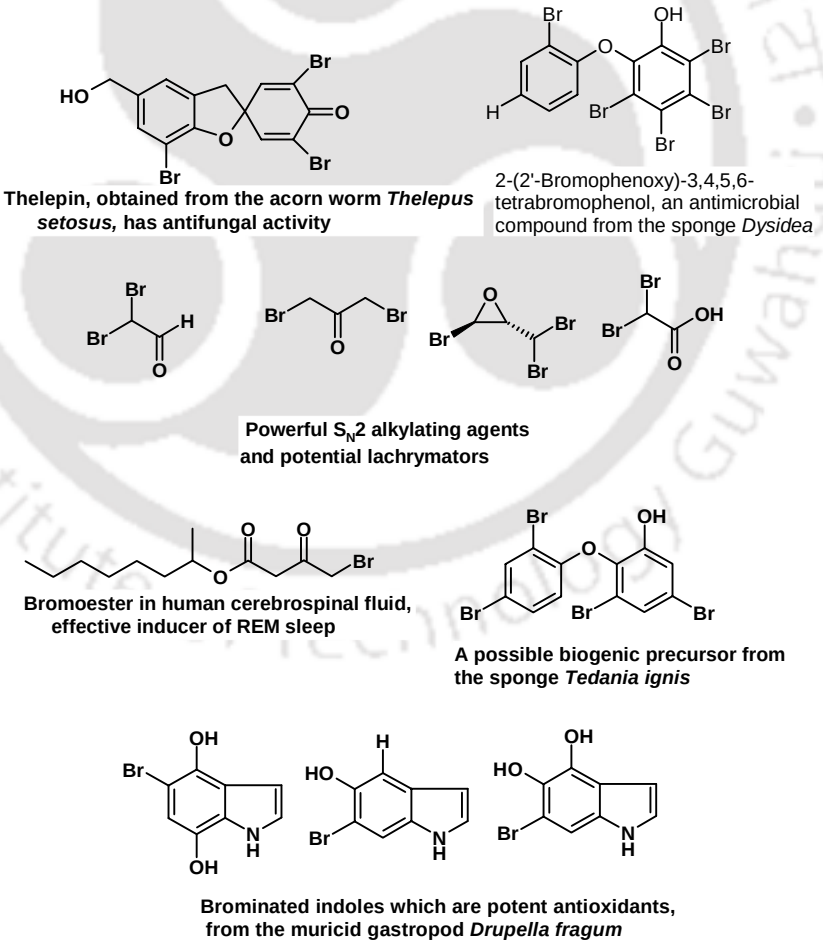


Figure 1.2 A Few Naturally Occurring Bromoorganic Compounds

Bromine is commonly used in most bromination reactions even though the reagent is extremely toxic and corrosive in both liquid and vapor forms. Moreover, the atom accountability in reactions involving bromine shows trends of inefficiency and waste. Therefore, what is now required is the identification of alternative reaction conditions and solvents for improved selectivity and energy minimization using less toxic and inherently safer chemicals, leading to the discovery and development of not only newer reagents but also newer synthetic pathways using environmentally benign chemistry.

While trying to bring the reaction chemistry of peroxovanadium complexes to the fore, the importance of synthesis of simple peroxo and heteroligand peroxovanadates cannot be underestimated. The synthetic peroxo-metal chemistry entailing structural characterization is as important as its reaction chemistry is. And both aspects must go ahead hand in hand. Guided by this strategic importance, in recent years there has been a remarkable advancement in the synthetic chemistry of peroxovanadium(V) through the endeavour of several groups of workers[33-36,39,54-62,84,98-100] Yet there exists a good deal of continued interest in the synthesis of newer diperoxovanadates(V) in specific heteroligand environment, as the biochemical significance and importance in the oxidation chemistry for the activation and oxygen transfer reactions renders the isolation of such compounds in the solid state highly sought after.

Synthesis and isolation in the solid state of peroxovanadium(V) compounds are sometimes tricky due to the uncertain nature of peroxovanadates(V) in solutions of varying pH.[83,101] While this is admittedly true, the problem of the synthesis of such compounds cannot be just shelved because they are needed for

understanding the coordination chemistry of the metal, biomodeling and developing practically useful catalytic systems. Peroxoheteroligand vanadate systems amenable to electronic spectroscopic studies[60] are also important as probes for the study of electronic structures of the metal-dioxygen unit,[60] particularly in relation to bonding of O_2 to the metal centers in metalloenzymes, oxygen-carrying proteins, and for the study of the peroxo-metal interactions in catalytic oxidations.[102-108] As mentioned earlier, our group has been involved in investigations of different aspects of peroxovanadium(V) chemistry [31-34,54-62,72-82] over the past two decades and as a part of the program it became incumbent on us to develop newer heteroligand diperoxovandates(V) as insulin mimics.

Insulin, it may be mentioned, is a very important hormonal regulator of fuel metabolism, and stimulates the storage of fuels and the synthesis of proteins in a variety of ways. There are three classes of vanadium complexes that have received major attention from the insulin-mimetic community. These include: (i) the simple vanadium salts, (ii) bis(maltolato)oxovanadium(IV) and related complexes and (iii) the peroxovanadium complexes.[109] Studies on insulin mimicking activity revealed that peroxovanadium(V) complexes, probably due to the synergistic action of vanadate and peroxide to mimic insulin activity,[110] are about 100-fold more potent than vanadate in facilitating the rapid metabolic effects of insulin.[111-114] The ability of diperoxovanadium compounds to mimic insulin was first reported in 1987 by Posner and co-workers,[115-117] and continuing work by several groups including ours has established that many of these complexes also have a significant pharmaceutical role to play. Notably important in this context is a very recent work of Crans *etal.* on their heteroligand

diperoxovanadate(V) complex, $[VO(O_2)_2imz]^-$, which has shown a very high insulin mimicking activity.[48] Similar heteroligand diperoxovanadates(V) are much sought after, though it may be rather difficult to gain an access to.

Quite apart from what have been overviewed so far, the study of fluorometal chemistry is another area of high topical importance.[118] The study of some chosen aspects of fluoro chemistry of different elements has been very close to our hearts for quite some time.[119-131] One of our main concerns has been the development of newer fluorochromate(VI) reagents for partial oxidation of organic substrates.[132-136] This is because partial oxidations of organic molecules is a diverse and widely used area of chemistry with applications in nearly all of the important fine and speciality chemicals industries as well as others that are involved in the manufacture of pharmaceuticals, agrochemicals and monomers.

Stoichiometric metal oxidants based on vanadium(V), molybdenum(VI), chromium(VI) and manganese(VII) are perhaps the most preferred oxidizing agents in chemistry. Among these, chromium(VI) oxidants have been accepted readily by synthetic chemists since they are easy to handle, inexpensive, quite selective in action and are 'off the shelf reagents'. Chromium(VI) oxide based oxidants have been used for many years with systems like sodium dichromate in aqueous sulfuric acid being used since the turn of the century.[137] Chromium(VI) oxide has also been used in combination with aqueous acetic acid and sulphuric acid and acetone (Jones oxidation)[138]; but the use of these systems was severely limited by over-oxidation. Another limitation of these oxidants has been that the reagent systems are so highly acidic that acid sensitive substrates often cannot withstand. In addition again there was a problem of limited miscibility of the

above-described systems in organic solvents. Thus it was the need for further improved oxidations, greater ease of isolation, enhanced solubility in organic solvents and milder acidity that shaped a course for the vast development of chromium(VI) reagents.

The era of the next generation Cr(VI) reagents then began. The development of these reagents is based on the philosophy that the oxidizing power can be moderated by complexing the chromium(VI) centered anion with another cationic species. A variety of Lewis bases were subsequently used to complex chromium trioxide with the goal of varying the specificity of the oxidation and over the years a host of successful reagents were developed. It should be mentioned here that the chromium(VI) oxide complexes with nitrogen heterocycles are milder, more selective oxidants than the acid-based reagent systems. Thus, Sarett and co-workers developed **Chromium(VI) oxide.(pyridine)$_2$** by adding chromium(VI) oxide to pyridine.[139] The reagent was very useful for the preparation of aromatic and α,β-unsaturated aldehydes, but the method was severely handicapped due to the work-up problems encountered during the isolation of products from pyridine. **Chromium(VI) oxide.(3,5-dimethylpyrazole)** was then developed by Corey *et al*.[140] The reagent was generated *in situ* by the complexation of 3,5-dimethylpyrazole with chromium(VI) oxide. Though a good oxidant for allylic C-H oxidations, this reagent has not gained popularity. The next important entry in the series was **Pyridinium chlorochromate, PCC, $C_5H_5NH[CrO_3Cl]$,** which was first developed by Corey and co-workers.[141] The yellow crystalline compound which can oxidize activated C-H bonds, C-C bonds, C-B bonds and halogenate enol silyl ethers, is fairly **stable in absence of moisture**. The reagent

is somewhat acidic in nature (pH = 1.75) and sometimes requires the reaction medium to be buffered by sodium acetate. This reagent, because of its ease of preparation and versatility, has become a household name in any synthetic organic chemistry laboratory. Several reviews[142] have been published on PCC-oxidation. However, there are a few limitations of this reagent, if one may mention. In particular a relatively short shelf-life in an ambient condition, and a relatively higher acidity. These pose hindrances at times. In the year 1982, Chaudhuri and co-workers, while investigating fluorochromate chemistry, reported the first synthesis of **Pyridinium fluorochromate, PFC, $C_5H_5NH[CrO_3F]$**.[132] This reagent is as reactive as **PCC** but less acidic (pH =2.45) and thus substrates with acid labile groups can be oxidized without using a buffer. It is a potentially strong oxidizing agent for primary and secondary alcohols and can oxidize activated C-H bonds under mild reaction conditions. The reagent is stable for a prolonged period retaining its identity intact. Its solubility profile is superior to **PCC**.[132] The reagent is X-ray structurally characterized with $[CrO_3F]^-$ ion having a distorted tetrahedral structure.[143] (Fig. 1.3)

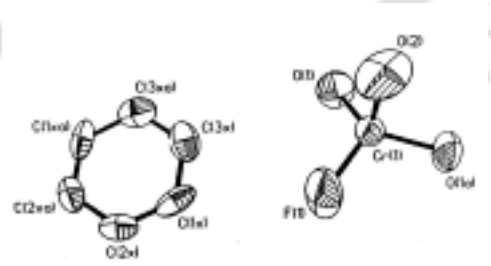


Figure 1.3. ORTEP Drawing of PFC Showing the Thermal Ellipsoids and Atomic Numbering Scheme. Hydrogen atoms are omitted for clarity

PFC is a selective oxidant and allows oxidation of secondary alcohols in presence of primary[144] and can be very efficiently used for the oxidative cleavage of the C-

B bond [145] and it can also be used for desilylative oxidation of alkyl trimethylsilyl ethers,[146] for instance. The track record reveals that the reagent has survived the test time with a sharp gain in popularity owing to its inherently important properties that are not encountered with the other Cr(VI)-based reagents.

A brief account may also be presented on the relatively less popular chromium(VI) reagents which include, **Bipyridinium chlorochromate (BiPCC), Quinolinium fluorochromate (QFC)** and **Pyridinium dichromate (PDC)**, for example. **BIPCC** was introduced as a mild, air stable nonhygroscopic oxidant.[147] The bipyridyl system acts as an internal buffer permitting the ready oxidation of alcohols in substrates with acid labile groups. It is however far weaker than **PCC** and higher equivalents of reagent are required for oxidations. **QFC** was reported[135] as a companion reagent of **PFC**, with some modified properties. Its pK_a was found to be 4.7, imparting to it a reduced acidic property. It has a relatively higher solubility in nonaqueous solvents. Although it is also a selective oxidant, it is yet to receive the kind of importance that **PFC** and **PCC** enjoy. **PDC** was developed by Corey *et al.* as an isolable, stable orange solid that can be easily and safely prepared.[148] It is a mild and selective oxidant, however, its limited solubility poses as a drawback. **PDC** is very soluble in solvents such as DMF, water and DMSO, but sparingly soluble in common organic solvents including chlorinated hydrocarbons and acetone. It is normally used either as a solution in DMF or as a suspension in dichloromethane.

Chromium(VI) oxidants, supported on alumina, silica, celite, polymer or resin, or adsorbed on carbon may sometimes have their reactivity and selectivity modified. Moreover these have the advantage that the residual chromium salts

remain bound to the support and thus work-up often becomes reduced to mere filtration. While overviewing the Cr(VI) reagents chemistry, the contribution of Muzart and coworkers can not be ignored. The work was mainly on allylic and benzylic oxidations,[149-152] though primary and secondary alcohol oxidations were also conducted in a few instances. The oxidants were used mostly as supported reagents barring a few cases of non-supported ones. Muzart's work also involved oxidant systems like a combination of chromium(VI)—peroxocarbonates[153,154] or chromium(VI)—peroxoborate.[155] Some advantages of these types of oxidants were emphasized.

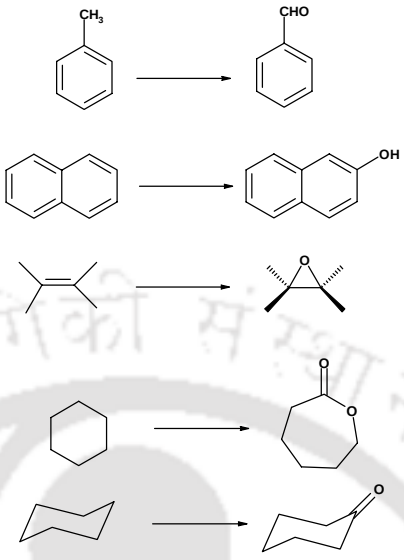
Unfortunately, even though a large number of chromium(VI) based reagents have been developed over the years, with each one having some advantages over the others, many of them seem to have certain drawbacks. These may include unsatisfactory performance in case of important transformations like oxidations of Δ^5-steroid, problematical work-up procedures, overoxidation in certain cases, decomposition of acid-sensitive substrates due to the acidic nature of some of the reagents or poor solubility and stability. One or more of these problems cause a reagent to become a non-performer in some selected cases of oxidations. In an attempt to circumvent these problems, the trend has been to develop newer reagents with improved properties and thus the search for a better performing reagent still continues.

Scope of Work

Having been rightly instigated by the hostility of chemical wastes and reckless disposal of unsafe chemical agents causing the environment to be unsafe for the human habitat and ecology in conjunction with the result of having been

influenced by the less clearly understood active principles of haloperoxidase in general (HPO) and vanadium bromoperoxidase (VBrPO) in particular, it became incumbent upon an **experimental chemist to address the issue of clean bromination of organic substrates**, the versatile applications and uses of which have already been highlighted, preferably by **using non-hazardous brominating agents** and by *in situ* **bromination of organic substrates including aromatic and heteroaromatic parent metabolites like phenols, anilines, and their derivatives**. This area of synthetic chemistry seems to be a rather hot issue involving quite a challenging problem that chemists and some chemical industries are now encountered with. Philosophically, the implied reactions fall in the regime of oxidative brominations of organic molecules. It is expected to provide knowledge of vanadium bromoperoxidase (VBrPO) activity through this investigation provided that vanadium is involved as the metal of choice and the reagents and protocols are articulated as VBrPO mimics.

While investigations pertaining to VBrPO activity and oxidative brominations are of topical importance, the partial oxidation of organic molecules (typically hydrocarbons and alcohols) is a diverse and widely used area of chemistry with applications in almost all of the fine and speciality chemicals industries including those manufacturing pharmaceuticals, agrochemicals and monomers, for example (Scheme 1.10):



Scheme 1.10. Some Important Partial Oxidation Reactions

Significantly, oxo-metal-based oxidants, especially, chromium(VI) and manganese(VII) perhaps qualify to be the best known oxidizing agents in chemistry which are so commonly used in both bench scale as well as on large scale partial oxidation reactions. An important point to be made here is that the use of such an oxidant on a large scale leads to a rather large volume of toxic metal waste. Not withstanding this, it is rather pleasantly surprising that such a reagent, e.g., a oxochromium(VI)-based oxidizing agent, continues to be used in many industrial processes. To mention just one is the conversion of secondary alcohol functions to ketones. A futuristic analysis causes one to believe that a high value addition of partially oxidized products obtained by using these reagents will continue to make the chemistry economically viable though it might not be environmentally benign. However, recycling of the chromium waste or its safe disposal (*c.f.* landfilled) is an alternative way to salvage the situation in the interest of bench scale chemistries as well as of large-scale industrial processes.

Thus**, interest on the efficacious oxochromium(VI) based reagents is certainly going to survive many more years and sustained activity in terms of greater efficacy, improved properties like controlled acidic character, enhanced stability and better solubility, for instance, are likely to draw special attention**. **Research addressing the problems highlighted above is not only in great demand but also rewarding**.

Whereas oxidative brominations and the other investigations related to the understanding of VBrPO and its activity are unquestionably very important, equally important is perhaps the studies related to the ability of peroxovanadium complexes to inhibit the activity of phosphotyrosine phosphatases and thus act as insulin mimics. For a variety of reasons peroxovanadium(V) compounds containing appropriate heteroligands are considered suitable candidates for insulin mimetic studies. Bis(peroxo)vanadium(V) imidazole complex, $ImzH[VO(O_2)_2(imz)]$, (Imz = imidazole), which has recently been shown to be the most potent insulinomimetic complex known as of now, attests to this assertion. Similar diperoxovanadate(V) species containing 3,5-dimethyl pyrazole (dmpz) as the heteroligand deserves the attention of vanadium chemists since such complexes are in all probability going to be at least as potential insulin mimics as the analogous imidazole containing peroxovanadium(V) complex is. This might be all the more rational because of the structural similarity betwen dmpz and imidazole. In addition, studies involving dmpz as a ligand may not be very trivial because dmpz complexes of vanadium(IV) or (V) seems to have been very little worked on. Thus, the coordination chemistry of V(V) —dmpz in the presence of peroxide deserves attention.

The present overview, including a critical assessment of the state-of-art of the problems addressed therein, provide reasons that are convincing enough to undertake studies addressing the identified problems that find roots in peroxovanadium(V) and oxochromium(VI) chemistries. In resonance with this the present Ph.D research was initiated in 1988 in order to investigate some of the above-mentioned problems. The nature of the problems is such that there have been significant developments in nearly every couple of months thereby rendering it rather difficult to keep pace with. The outcome of our endeavour has finally led to the following end results:

(i) The development of clean brominating agents viz., quaternary ammonium tribromides with QA = tetramethylammonium (**TMA**), tetraethylammonium (**TEA**), tetrabutylammonium (**TBA**) and cetyltrimethylammonim (**CTMA**) and TB = Br_3^-, by peroxovanadate(V) catalyzed oxidation of Br^- to Br_3^- in a weakly acidic medium in the presence of a quaternary ammonium ion, and benign protocols for oxidative bromination of organic substrates promoted by vanadium(V) — H_2O_2. **An interpretative account of this work has been presented in two parts (A and B) in Chapter 3**.

(ii) The synthesis and characterization of a set of new heteroligand diperoxovanadates(V) containing 3,5-dimethyl pyrazole as the chosen hetero-ligand, viz., **DmpzH[VO(O$_2$)$_2$(dmpz)]**, **K[VO(O$_2$)$_2$(dmpz)].H$_2$O**, **NH$_4$[VO(O$_2$)$_2$(dmpz)].H$_2$O** and **Na[VO(O$_2$)$_2$(dmpz)].2H$_2$O** have been completed successfully. **The results obtained from this exercise constitute the subject matter of Chapter 4**. These compounds have

been prepared with intent to develop newer insulin mimics and investigate their activity.

(iii) The development of 3,5-dimethylpyrazolium fluorochromate(VI) (**DmpzHFC**), $C_5H_8NH[CrO_3F]$, as a new chromium(VI) reagent, especially suitable for oxidation of Δ^5-steroids and 6-methoxy tetralene. These substrates are important as Δ^5-7-ketones are found in animal tissues and food stuffs and are known to be inhibitors of mammalian sterol biosynthesis and cell replication, while 6-methoxy-1-tetralone appears to be the key building block for several life saving drugs and steroid molecules, whereas their accessibility is really difficult. The reagent, **DmpzHFC**, is also very efficient for oxidation of other substrates like alcohols, polycyclic hydrocarbons, triphenyl phosphine and so on. It has been ascertained that the reagent works as a two-electron oxidant. **Detailed information covering all aspects of this investigation is incorporated in Chapter 5**, which is indeed the concluding Chapter of the thesis.

In addition to this Chapter (i.e., **Chapter 1**) which introduces the identified problems for the Ph.D research, provides an overview of the status of the problem, and also pin points the scope of work, **Chapter 2** describes the sources of chemicals and solvents that were used in the work, methods of preparation of a few starting materials, details of the methods of chemical analyses, and particulars of various instruments and equipment used for physico-chemical studies and characterization of the reported compounds. Each Chapter from 3 through 5 has been deliberately designed to be self-contained having a brief

introduction and sections on experimental, and results and discussion followed by bibliography. While some of the results have been published, manuscripts based on the rest are either under communication or preparation.

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METHODS OF PREPARATION OF STARTING MATERIALS, ELEMENTAL ANALYSES AND THE DETAILS OF INSTRUMENTAL TECHNIQUES USED FOR CHARACTERIZATION AND STRUCTURAL ASSESSMENT OF THE COMPOUNDS

Chapter 2

Detailed procedures adopted for the preparation of different starting materials are described in this chapter. Also described herein are the details of the methods used for quantitative determination of various constituents and the relevant particulars of the instruments/equipment used for the characterization and structural assessment of the newly synthesized compounds.

All the chemicals and solvents used for the present work were of analytical grade quality. Following are the sources of the chemicals and solvents: s.d.fine-chem ltd, Qualigens Fine Chemicals, E.Merck (India) Limited, Sisco Research Laboratories Pvt. Ltd, Central Drug House (P) Ltd, Bengal Chemicals and Pharmaceuticals Ltd, Loba Chemie Industries, and Spectrochem (India).

Preparation of starting materials

3,5-dimethylpyrazole (dmpz)[1]

A methanolic solution of 25 mL of hydrazine hydrate, $N_2H_4.H_2O$, (25.0 g, 499.4 mmol) was added slowly with stirring to a methanolic solution of 25 mL of acetylacetone (25.0 g, 249.7 mmol) in an ice-cold condition. A light yellow solution was obtained. The solution was concentrated to *ca.* 20 mL on a steam-bath and left overnight in a refrigerator. A white crystalline compound was obtained and this was isolated by filtration, washed 4 or 5 times with water and dried in air. The yield of pure 3,5-dimethylpyrazole (dmpz) was 23.5 g (98 %). M.p. 107 – 108 °C (lit. m.p. 107 – 109 °C).

Benzylideneacetophenone (Chalcone or 1,3- diphenylprop-2-en-1-one)[2]

A solution of 22 g of sodium hydroxide was prepared in 200 mL of water and 100 g (122.5 mL) of ethanol in a 500 mL bolt-head flask provided with a mechanical stirrer. The flask was immersed in a bath of crushed ice, and poured in 52 g (430 mmol) of freshly distilled acetophenone. To the solution was added 46 g (44 mL, 430 mmol) of pure benzaldehyde under continuous stirring. The temperature of the mixture was maintained at *ca.* 25 °C and stirred vigorously for 2 or 3 h until the mixture became so thick that stirring was no longer effective. The stirrer was removed and the reaction mixture was left in an ice chest or refrigerator overnight. The product was filtered under suction on a Buchner funnel or a sintered glass funnel and washed with cold water until the washings were neutral to litmus, and then with 20 mL of ice-cold ethanol. The air-dried crude chalcone weighed 88 g and melted at 50-54 °C. This was then recrystallised from warm ethanol. The yield of pure benzylideneacetophenone (a pale yellow solid) was 77 g (85 %). M.p. 56 or 57 °C (lit. m.p., 55 – 57 °C.) (*The substance should be handled with care since it is a skin irritant.*)

3-(4-Methoxy-phenyl)-1-phenyl-propenone

The method of preparation 3-(4-Methoxy-phenyl)-1-phenyl-propenone was similar to that of 1,3-diphenylprop-2-en-1-one except that to the stirred solution of acetophenone in sodium hydroxide, 58.54 g (52.31 mL, 430 mmol) of pure 4-

methoxy benzaldehyde was added instead of benzaldehyde. Yield of the pure product was 71.7 g (70 %), M.p. 76 °C (lit. m.p., 77 or 78 °C).[3]

Methyl Cinnamate (3-methoxy-1-phenyl-propenone)[4]

An amount of 59 g (400 mmol) of cinnamic acid is added to a solution of 128 g (162 mL, 4000 mmol) of dry methanol and 6 mL of concentrated sulphuric acid, and the whole was refluxed for 5 h. The excess methanol was removed and the residue was poured into *ca.* 500 mL of water. To this was added 300 mL of ether. The ether solution was separated, washed and dried in the usual way. The ether was removed on a rotary evaporator. On cooling, the residue crystallized yielding 58 g (90%) of methyl cinnamate. M.p. 33 or 34 °C. To obtain the pure product having melting point 36 °C, the sample was dissolved in a minimum amount of methanol being maintained at 30 °C on a warm water bath. To this, water was added slowly, from a dropping pipette, with stirring until the oily ester just began to separate. The solution was seeded and transferred rapidly to an ice bath with a glass rod. On scratching the walls of the vessel vigorously with a glass rod, crystals began to appear. The resulting colourless needles were filtered rapidly and dried in air. Yield 51.5 g (80 %).

Potassium metavanadate (KVO_3)[5]

An amount of 69.11 g (500 mmol) of potassium carbonate was dissolved with stirring in 400 mL of water contained in an 800 mL beaker. The solution was maintained at 85 – 90 °C by heating on a hot water-bath or a well-adjusted hot plate. To the clear

colourless solution was added, in small portions, under heating and constant stirring, 90.95g (500 mmol) of vanadium(V) oxide. (*Caution: The effervescence may result in a tan to dark-brown opaque mixture*) When the effervescence subsided, 10 mL of 3% H_2O_2 was added to assist dissolution of the vanadium oxide by oxidizing the small proportion of the vanadium(IV) that is generally present in the commercial product. The reaction mixture was maintained at 85 – 90 °C with constant stirring for *ca.* 2.5 h during which time the volume was reduced to 150-200 mL by evaporation. The mixture was heated to just below boiling and then filtered immediately by suction through a 9 cm coarse-porosity fritted glass funnel (*the mixture was too viscous to be filtered through filter-paper*) into a 500 mL filter flask. The coarse brown to black residue, if any, was discarded. A boiling chip was added to the filter-flask containing the clear light yellow and slightly viscous filtrate. The exact colour of the solution depended upon the pH (*A deep yellow colour would indicate that too little K_2CO_3 had been used while colourless solution would indicate that too much K_2CO_3 has been used*). The flask was stoppered and evaporated with aspirator suction on a hot (85 – 90 °C) water bath (*Use of hot-plate might decompose the product*). The solution became increasingly viscous and suddenly a nearly white precipitate began to form. The volume of the mixture was reduced to *ca.* 75 mL and the powdery pale-yellow precipitate was collected on a 9 cm fritted-glass funnel, washed first with 20 mL of 95% ethanol, and finally air-dried. The yield of the powdery pale-yellow product was 40 g (29%). When the reaction mixture was evaporated to a volume of *ca.* 25 mL, a second crop of the product (*ca.* 30 g, *ca.* 20%) was also obtained.

Elemental analyses

Vanadium[6]

Vanadium was estimated iodometrically.

An accurately weighed amount (*ca.* 0.1 g) of vanadium compound was dissolved in 100 mL of water. To the solution was added 5 mL of 5M H_2SO_4. The solution was boiled for 10 min to remove peroxide. To this solution was added 5 g of potassium persulphate followed by the addition of one drop of silver nitrate, $AgNO_3$, solution. The resultant mixture was boiled for 1 h. After this 15 mL of 5M H_2SO_4 was added and the solution boiled for a further period of 30 min. The solution was allowed to cool to room temperature and *ca.* 5 g of KI was added with stirring. This was then kept in the dark for 15 min. The liberated iodine was then titrated with standard $Na_2S_2O_3$ solution using starch as an indicator. The end point was detected by the appearance of a light-blue colour.

1 mL of 0.1 M $Na_2S_2O_3$ = 0.00519 g of vanadium

Chromium[7]

Chromium was estimated iodometrically.

An accurately weighed amount (*ca.* 0.1 g) of a chromium(VI) compound was dissolved in water (*ca.* 120 mL) by slight warming. The solution was cooled to room temperature and acidified with 10-12 mL of 5M H_2SO_4 followed by the addition of *ca.* 3 g of KI with stirring. The whole was kept in the dark for *ca.* 15 min. The liberated iodine was titrated with standard sodium thiosulphate solution in carbon dioxide atmosphere.

1 mL of 0.1 M $Na_2S_2O_3$ = 0.0052 g of chromium

[In case of lowervalent chromium compound (say Cr(IV), it was first oxidized to chromium(VI) with a silver catalyzed persulfate oxidation and then proceeded for estimation.]

Sodium and Potassium[8]

Sodium and potassium contents were determined by flame photometry. A solution containing sodium or potassium ions was acidified with hydrochloric acid. The acidified solution thus obtained was used for flame photometry.

Fluoride[9]

An accurately weighed amount (*ca.* 0.1 g) of fluoride containing compound of chromium was dissolved in 150 mL of water. The solution containing fluorochromate(VI) compound was boiled with 20 – 25 mL of 0.1 M NaOH for *ca.* 30 min. Hydrazine monohydrate was then added to the warm solution drop by drop to reduce Cr(VI) to Cr(III) and precipitate the metal as hydrated Cr(III)oxide [*c.f.* $Cr(OH)_3$]. The solution was digested on a steam bath for *ca.* 30 min. and filtered to separate the hydrated oxide. The residue was washed thoroughly with water. To the combined filtrate and washings, two or three drops of bromophenol blue indicator and 3 mL of a 10% sodium chloride solution were added and diluted to *ca.* 250 mL. 6 M nitric acid was added to it until the colour just changed to yellow, followed by the addition of 0.1 M NaOH solution until the colour changed to blue. The mixture was then treated with 1 mL of conc. HCl and 5 g of $Pb(NO_3)_2$ and heated on a steam-bath. After all the lead nitrate had dissolved, 5 g of crystallised sodium acetate was added

to the solution and the solution digested on a steam-bath for *ca.* 30 min. with occasional stirring and then allowed to stand overnight.

The precipitate was filtered through a Whatman 542 filter paper, washed five or six times with water to make it free from chloride. The precipitate was dissolved in 1% HNO_3 by slight warming. A known excess of standard $AgNO_3$ (0.1 M) solution was added and the suspension of AgCl heated almost to boiling and stirred vigorously. The beaker and its contents were kept in the dark for 1 h, the precipitated AgCl was filtered out and washed with water. The unreacted $AgNO_3$ was finally titrated with standard KSCN solution using $Fe(NO_3)_3$ as indicator. The end point was marked with the appearance of a faint-red brown colour. The volume of $AgNO_3$ in the filtrate thus found was subtracted from the amount that originally added. The fluoride content was calculated from the volume of $AgNO_3$ solution consumed.

1 mL of 1 M $AgNO_3$ = 0.019 g of fluoride

Bromide[10]

Bromide was estimated volumetrically following Volhard's method.

An accurately weighed amount (*ca.* 0.1 g) of organicammonium tribromide was dissolved in 20 mL of acetonitrile. The solution was treated with 20 mL of a 20% NaOH solution, followed by the addition of 100 mL of water. The solution was boiled for 1 h and acidified with dilute (1:1) HNO_3. The acidified bromide solution was then treated with an excess of 0.1 M silver nitrate solution. The suspension was heated almost to boiling and stirred vigorously. The beaker along with the suspension was kept in the dark for 30 min. The precipitated AgBr was separated out by filtration and

washed several times with water. The filtrate and the washings were collected and the unreacted $AgNO_3$ was titrated with standard KSCN solution using $Fe(NO_3)_3$ as indicator. The end point was marked by the appearance of a faint red – brown colour. From the equivalence of standard $AgNO_3$ and standard KSCN solutions, the volume of excess $AgNO_3$ was calculated and this was subtracted from the volume of $AgNO_3$ initially added. The difference is the volume of $AgNO_3$ solution consumed.

1 mL of 1 M $AgNO_3$ = 0.0799 g of bromide

Peroxide

(a) Permanganometry[11]

Nearly 1 g of boric acid was dissolved in 100 mL of water taken in a conical flask. To this was added an accurately weighed amount (*ca.* 0.1 g) of peroxo compound followed by the addition of 7 mL of 5M H_2SO_4. The solution was shaken well to dissolve the compound. The peroxide was then estimated by redox titration with standard $KMnO_4$ solution. The end point was marked by the appearance of a permanent faint pink colour.

1 mL of 0.2 M $KMnO_4$ = 0.016 of peroxide

(b) Iodometry[12]

To a freshly prepared 2 M sulphuric acid solution, containing an appropriate amount of potassium iodide (~2 g in 100 mL) was added an accurately weighed amount (*ca.* 0.1 g) of a peroxo compound with stirring. The mixture was allowed to stand for *ca.* 15 min in carbon dioxide atmosphere in the dark. The amount of iodine liberated was then titrated with a standard sodium thiosulphate solution, adding 2 mL

of freshly prepared starch solution when the colour of the iodine was nearly discharged.

$$1\ mL\ of\ 1N\ Na_2S_2O_3 = 0.01701\ g\ of\ peroxide\ (O_2^{2-})$$

[In case of a peroxovanadate(V) complex, this method gives the total amount of peroxide plus vanadium present in the compound. On deduction of the contribution of vanadium (V) from the total amount of iodine liberated, the net peroxide content of the compound is evaluated.]

Carbon, Hydrogen and Nitrogen

The carbon, hydrogen and nitrogen contents were estimated by micro-analytical methods. The results of the analyses were obtained using a 2400 Perkin Elmer Series II CHNS/O Analyzer. The results were obtained from the Micro Analysis Laboratory, IACS, Calcutta 700032, and IIT Guwahati, Guwahati 781039.

Particulars of Instruments/Equipment Used for the Following Physico-chemical Studies

pH Measurement

pH values of the reaction solutions were recorded with a Systronics Type 335 digital pH meter and also by using Merck pH indicator paper.

Solution Electrical Conductance Measurement

Solution electrical conductance measurements were measured on a Systronics Type 304 direct digital reading conductivity meter. Solution strength was maintained at 10^{-3} M in appropriate solvents.

Recording of Melting Point

Melting points of the compounds were recorded using a MP1 V-Scientific melting point apparatus and a Type B-540 Buchi melting point apparatus. The heating rate was maintained at either 5 °C or 10 °C.

Infrared Spectroscopy

Infrared spectra of the compounds were recorded *as* KBr pellets, as nujol mulls or as thin films using a Nicolet Impact–410 Fourier Transform Infra Red Spectrophotometer, or on a Perkin-Elmer model 983 Spectrophotometer. For recording the spectra below 400 cm^{-1} regions, polyethylene powder was used as the medium.

Electronic Absorption Spectroscopy

UV-visible spectra were recorded, by dissolving a calculated amount of the sample in an appropriate solvent, on a Hitachi UV – visible U–2001 Spectrophotometer.

^{1}H Nuclear Resonance Spectroscopy

^{1}H NMR spectra were recorded either on a Bruker 300 MHz or a Varian 90 or 300 MHz NMR spectrophotometer using tetramethylsilane (TMS) as internal standard. These were recorded at the Regional Research Laboratory, Jorhat, the

Regional Sophisticated Instrumentation Centre, Shillong, and at the Indian Institute of Chemical Technology, Hyderabad.

Thermal Studies

Thermogravimetry (TG) and Differential Scanning Calorimetry (DSC) experiments were conducted on a Mettler-Toledo TGA/SDTA 851^e and DSC 821^e instruments. Experiments were done using either aluminium or platinum crucibles. Pure N_2 gas was used as the flow gas.

Mass Spectrometry

Mass spectrometric analysis was done using GC-MS Fission 5000, EI mode (70 eV) instrument (Quadruple Mass Spectrometer).

Gas Chromatography

Gas chromatographic analysis was done on a Hewlett Packard HP 6890 GC system with the aid of an FID detector by using a SE-30 capillary column. In all cases, nitrogen gas was used as a carrier gas. The results were recorded on an HP 3395 integrator.

X-ray Crystallography

X-ray quality crystals were obtained for $[VO_2F(dmpz)_2]$ (*vide* Chapter 4). Single crystal X-ray data on it were collected at room temperature on Enrauf-Nonius CAD4-Mach diffractometer using graphite-monochromated MoKα radiation (λ=0.71073 Å). The cell parameters in each case were determined by least-squares

refinement of the diffractometer setting angles for 25 centered reflections that were in the range 22 $^{o}\leq 2\theta \leq 25^{o}$. For the compound, the systematic absences were consistent with the space group C_c. The structure was solved and successfully refined in the space group C_c. Three standard reflections were measured at every hour to monitor instrument and crystal stability. The maximum corrections of intensity based on the standard reflections were less than 1% for each. Intensity data were corrected for Lorenz and polarization effects; analytical absorption corrections were applied. The XTAL 3.2 program package was used in absorption and all subsequent calculations, utilizing a 486-DX personal computer (PCL, India) operating at 66 MHz under MS-DOS version 5. The linear absorption coefficients, scattering factors for the atoms, and the anomalous dispersion corrections were taken from the International Tables for X-ray crystallography. The structure was solved by the direct method and successive difference Fourier syntheses. The refinement was done by full-matrix least squares techniques using anisotropic thermal parameters for all non-hydrogen atoms. Some of the H-atoms could be located in the difference maps in each case, the rest were calculated assuming ideal geometries of the atom concerned. H atom positions or thermal parameters were not refined.

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PEROXO-METAL MEDIATED ENVIRONMENTALLY FAVOURABLE ROUTE TO BROMINATING AGENTS AND PROTOCOLS FOR BROMINATION OF ORGANICS

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A part of the work described in this Chapter has been pulished:

(i) *Organic Letters*, **2000**, *2*, 247.
(ii) *Patent accepted*, 28/CAL/2000 of 19-01-2000.
(iii) *Pure Appl. Chem.*, **2001**, *73*, 93.

Chapter 3

Although bromoorganics take a rather small share of the entire domain of organic chemistry, brominated organic products, especially bromoaromatics enjoy a very special status because of their use in the manufacture of a range of bulk and fine chemicals including flame-retardants, disinfectants, antibacterial and antiviral drugs.[1] The commercial importance of organic bromo derivatives lies in their use as precursors in the manufacture of pharmaceuticals, agrochemicals and other specialty chemical products. All these and some other applications have rendered this branch of chemistry to be one of those much sought after areas of contemporary importance.[2,3]

General methods that are largely used in practice involve elemental bromine (Br_2) because of its cost-effectiveness and versatility, even though elemental bromine in any of its forms is very detrimental to health and hazardous to the environment. Also the noxious and corrosive nature of Br_2 in both liquid and vapor form makes its transportation, storage and handling extremely difficult and risk proned.[4-6] Under the given situation, economically viable routes to bromination of organics with the adaptation of eco-friendly routes are necessarily going to be the protocols of choice.

Interestingly, marine natural chemicals contain bromometabolites such as halogenated phenols, terpenes, C-15 acetogenins and indoles, for example,[7] which are generated through VBrPO catalyzed bromination of the metabolites. It is also understood from the knowledge obtained from the structure and reactivity studies of VBrPO that the enzyme interacts first with H_2O_2 to activate the coordinated peroxide ligand so as to enable it oxidize bromide that is available in the marine natural

system to produce active bromine species which in turn is responsible for bromination of organic substrates in the marine environment.[8]

Bromometabolites are important as they are responsible for providing defense mechanism to the marine lives.[9] What is equally interesting to note is that the metal, vanadium occurs in its pentavalent state in VBrPO and that it does not undergo any redox cycling in the catalytic bromination process.[10,11] Co-incidentally, laboratory experiments involving pre-synthesized peroxovanadates(V) complexes suggest that peroxovanadium(V) intermediates also transform bromide (Br^-) to one or more of its oxidized forms.[12] Several groups of researchers [12-15] believe that an oxidized bromide exists in solution as:

$$OBr^- \leftrightarrows Br_2 \leftrightarrows Br_3^-$$

The time scale of the reactivity studies maintained in our experiments provided firm evidence for the formation of tribromide (Br_3^-) as the oxidized form of Br^-. What was also observed was that like in the VBrPO reactions, V(V) center did not undergo any reduction but retained its identity in so far as its oxidation state is concerned. And an appropriate acidity of the reaction solution is a prerequisite for bromide oxidation. Knowledge obtained from such studies in conjunction with the existence of Br_3^- in solution (λ=267 nm)[16-18] in high concentration caused us to believe that Br_3^- could be not only generated in solution but also isolated in the solid state by providing an appropriate counter cation. This knowledge guided us to develop an eco-friendly general route to the synthesis of quaternary ammonium tribromides (**QATBs**) with QA being tetramethylammonium (**TMA**), tetraethylammonium (**TEA**), tetrabutylammonium (**TBA**) or

cetyltrimethylammonium (**CTMA**) followed by probing their efficacy as very effective brominating agents. An interpretative account of these results constitutes **Part A** of this Chapter. While tribromide (Br_3^-) is capable of being isolated as indicated above, one could make a good use of this species (Br_3^-) by generating it in solution and then using this as an active brominating species *in situ* to devise a protocol for bromination of organic substrates, a philosophy that parallels the VBrPO activity. The results of our success in this endeavor have been described in **Part B** of Chapter 3.

Part A

Quaternary Ammonium Tribromides (QATBs) [QA = Tetramethylammonium (TMA), Tetraethylammonium (TEA), Tetrabutylammonium (TBA) and Cetyltrimethylammonium (CTMA); TB = Br_3^-] : Clean Synthesis, Characterization and Efficacy of QATBs as Brominating Agents

The fact that hydrogen peroxide (H_2O_2) on being coordinated to a higher valent transition metal (e.g., V(V), Mo(VI), W(VI), Ti(IV), Cu(II) or UO_2^{2+}) gets activated to perform many reactions and bring about transformations which are either not possible by hydrogen peroxide alone or very sluggish to be of any practical utility is now well accepted.[19] This strategy is used not only by chemists and technologists for laboratory scale reactions as well as commercial manufactures but also by the nature in bringing about numerous transformations.[20] One such example of the latter type is the vanadium haloperoxidase (VHPO) activity[8,10] in the domain of marine natural products biosynthesis. Isolation of the enzymes vanadium chloroperoxidase (VClPO)[21] and vanadium bromoperoxidase (VBrPO),[22,23] especially the latter, in conjunction with the investigations addressed to their reactivity profiles[7,8,10,13,24] unraveled various facets of these enzymatic reactions. As a case in point, for instance, VBrPO catalyzed bromination of organic marine chemicals including bromometabolites like phenols and anilines are very important biotransformations. The overall understanding is that VBrPO catalyzes the hydrogen peroxide oxidation of bromide (Br^-) to afford 'Br^+' (HOBr = Br_2 = Br_3^-) as the active

brominating species that in turn brominates organic substrates in marine aquatic conditions.[10] While this knowledge was gaining ground, we were already involved in the investigation of chemistry of peroxometals especially in terms of their synthesis, spectroscopic characterization, and reactivity studies.[25-30] What attracted our attention at that juncture were the bromide oxidation as mentioned above, the importance of bromoorganics as highlighted in the preamble, environmental problems associated with classical brominations by Br_2, and the capability of many peroxocomplexes of Ti(IV), V(V), Mo(VI) and UO_2^{2+} to oxidize Br^- very effectively in the presence of an acid.

Having been intrigued by these developments, we embarked on the investigation of peroxometal-catalyzed oxidation of bromide (Br^-) with intent to generate further information about the VBrPO mimicking activity. Apart from probing into the identity of the oxidized bromide species formed in solution by electron-absorption spectroscopy and then isolation of the oxidized bromide species, we were keen to develop clean brominating agents in a relatively safer way, in keeping with the tenets of Green Chemistry[31] as far as possible.

This part of the present chapter (i.e., Part A of Chapter 3) deals with the essentials of a benign route to the synthesis of tetramethylammonium tribromide (**TMATB**), Me_4NBr_3, tetraethylammonium tribromide (**TEATB**), Et_4NBr_3, tetrabutylammonium tribromide (**TBATB**), Bu_4NBr_3 and cetyltrimethylammonium tribromide (**CTMATB**), $(cet)(Me)_3NBr_3$, and their characterization by physicochemical methods, including a direct reference to the X-ray crystallographically determined structure of (**TBATB**), Bu_4NBr_3. Also presented

herewith are a few bromination reactions, conducted in acetonitrile as the solvent, to ascertain their efficacy. Also a comment has been made on the relative bromination efficacies of the four tribromides. Incidentally, for the synthesis of **CTMATB** there does not seem to be any literature precedence, let alone any bromination involving it, but for a very brief mention in a patent abstract[32] emphasizing on its antibacterial properties.

EXPERIMENTAL SECTION

All the chemicals used were of reagent grade. The sources of the chemicals and solvents have all been already given in Chapter 2. Quantitative determination of elements was accomplished by the methods described in Chapter 2. The details of all the equipment used for physico-chemical studies are also provided in Chapter 2.

SYNTHESIS OF QUATERNARY AMMONIUM TRIBROMIDES (QATBs)

Synthesis of Tetramethylammonium Tribromide (TMATB), $(CH_3)_4NBr_3$

Method I. An amount of 0.19 g (1.6 mmol) ammonium metavanadate (NH_4VO_3) was added to 20 mL (176.47 mmol) of 30 % hydrogen peroxide (H_2O_2), taken in a pre-cooled 250 mL beaker. The solution was stirred magnetically at 0-5°C till a clear red solution was obtained. To the solution, maintained at the same temperature as above, was added an acidic solution of 5 g (32.47 mmol) of tetramethylammomium bromide (TMAB) and 15.5 g (130.25 mmol) of potassium bromide (KBr) in 50 mL of 0.5 M sulphuric acid (H_2SO_4). The reaction mixture was stirred when orange compound started precipitating out.

$$\textbf{TMAB} \xrightarrow[H^+ / KBr]{V(V) / H_2O_2} \textbf{TMATB}$$

When precipitation was complete, the compound was filtered by suction filtration and dried in a vacuum desiccator using anhydrous calcium chloride ($CaCl_2$) as desiccant. The yield of the product obtained was 6.4 g, (63 %). M.p. 117 - 118 °C. (lit. m. p. 118 – 119 °C)[33]

Method II. An amount of 0.06 g, 0.32 mmol molybdic acid monohydrate ($H_2MoO_4.H_2O$), was added to 20 mL (176.47 mmol) of 30% hydrogen peroxide (H_2O_2) taken in a pre-cooled 250 mL beaker. The mixture was stirred at 0 – 5 °C temperature in an ice-water bath till all the molybdic acid dissolved and a clear yellow solution was obtained. To it was added a solution of 15.5 g (130.25 mmol) of potassium bromide (KBr) and 5 g (32.47 mmol) of tetramethylammonium bromide (TMAB) dissolved in 50 mL of 0.8 M sulphuric acid (H_2SO_4). The solution was stirred magnetically in an ice-water bath till an orange-yellow crystalline precipitate started appearing. The beaker containing the reaction mixture was then cooled in a refrigerator for further precipitation to occur.

$$\textbf{TMAB} \xrightarrow[H^+ / KBr]{Mo(VI) / H_2O_2} \textbf{TMATB}$$

The total amount of the crystalline orange-yellow product was obtained in three crops. The filtrate obtained after isolation of the first crop by suction filtration on being cooled again in the refrigerator afforded the second crop that was isolated in a manner similar to that of the first crop. The third and final crop of the product was obtained on repetition of the procedures once again. The compound was dried in a

vacuum desiccator using anhydrous calcium chloride ($CaCl_2$) as desiccant. The product was obtained as bright yellow micro-crystals. The yield of the compound was 9.4 g, (i.e., 92 %). The compound melted at 117 - 118°C. (lit. m. p. 118 – 119°C)[33]

Method III. An amount of 0.08g (0.44 mmol) molybdic acid monohydrate ($H_2MoO_4.H_2O$) was dissolved in 30 mL (264.91 mmol) of 30 % H_2O_2 and the mixture was stirred for *ca.* 30 min at 0-5 °C to get a clear yellow solution. To this was added a solution of 5 g (45.64 mmol) of tetramethyl-ammonium chloride (TMAC) and 32 g (268.91 mmol) of potassium bromide (KBr) with both being dissolved in 100 mL of 1 M H_2SO_4. The reaction mixture was stirred whereby an orange coloured crystalline compound immediately precipitated out.

$$\textbf{TMAC} \xrightarrow[H^+ / KBr]{Mo(VI) / H_2O_2} \textbf{TMATB}$$

The reaction mixture along with the precipitate was kept cooling at ~4 °C for 12 h. The compound formed in this process was isolated by suction filtration and dried *in vacuo*. The isolated yield of the product was 12.96 g (90.4 %). M.p. 117 - 118 °C. (lit. m. p. 118 – 119 °C)[33]

Synthesis of Tetraethylammonium Tribromide (TEATB), $(C_2H_5)_4NBr_3$

An amount of 0.05 g (0. 27 mmol) of vanadium pentoxide, V_2O_5, was added to 5 mL (44.12 mmol) of 30% hydrogen peroxide (H_2O_2) taken in a pre-cooled 250 mL beaker (*Care should be taken to maintain ice-cold condition as the reaction between V_2O_5 and H_2O_2 is exothermic*). The reaction mixture was stirred at 0 – 5 °C

temperature in an ice-water bath till all the V_2O_5 dissolved and the solution became reddish-brown. To it was added a solution of 5.67 g (47.65 mmol) potassium bromide (KBr) and 5 g (23.81 mmol) of tetraethylammonium bromide (TEAB), dissolved in 25 mL of 1M H_2SO_4. An orange-yellow precipitate started to appear after 5 minutes of stirring. The mixture was stirred continuously for about 30 minutes subsequent upon which the whole was kept standing in an ice-bath for ~ 1h, to give a bright yellow orange coloured compound.

$$\textbf{TEAB} \xrightarrow[H^+ / KBr]{V(V) / H_2O_2} \textbf{TEATB}$$

The product thus formed was isolated in a manner as that in the previous procedure. The compound was then dried in a vacuum desiccator using anhydrous calcium chloride, $CaCl_2$ as desiccant. The product was obtained as bright orange micro-crystals with the yield being 8.6 g (98 %). M.p. 85 - 86 °C.

Synthesis of Tetrabutylammonium Tribromide (TBATB), $(C_4H_9)_4NBr_3$

An amount of 0.05 g (0. 27 mmol) of vanadium pentoxide, V_2O_5, was added to 5 mL (44.12 mmol) of 30% hydrogen peroxide (H_2O_2) taken in a pre-cooled 250 mL beaker (*Care should be taken to maintain ice-cold condition as the reaction between V_2O_5 and H_2O_2 is exothermic*). The reaction mixture was stirred at 0– 5 °C temperature in an ice-water bath till all the V_2O_5 dissolved and the solution became reddish-brown. To it was added a solution of 3.7 g (31.09 mmol) of potassium bromide (KBr) and 5 g (15.53 mmol) of tetrabutylammonium bromide, TBAB, dissolved in 35 mL of water. To this, 50 mL of 1M sulphuric acid (H_2SO_4) was

added in small portions. Magnetic stirring was continued for a further period of 2 h at ice-water temperature. The product thus formed was isolated by suction filtration using Whatman 1 filter paper.

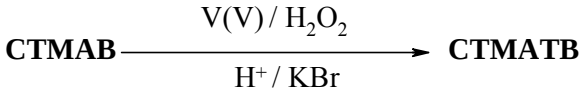
$$\textbf{TBAB} \xrightarrow[H^+ / KBr]{V(V) / H_2O_2} \textbf{TBATB}$$

The compound was then dried in a vacuum desiccator using anhydrous calcium chloride ($CaCl_2$) as desiccant. The product was obtained as bright yellow micro-crystals. The yield of the product was 7.4 g (99.5 %). M.p. 75 °C (lit. m. p. 76 °C).[16]

Synthesis of Cetyltrimethylammonium Tribromide (CTMATB), $(C_{16}H_{33})(CH_3)_3NBr_3$

An amount of 0.34 g (0.06 mmol) vanadium pentoxide (V_2O_5) was added to 5 mL (44.15 mmol) 30% hydrogen peroxide (H_2O_2) taken in a pre-cooled 100 mL beaker (*Care should be taken to maintain ice-cold condition as the reaction between V_2O_5 and H_2O_2 is exothermic*). The reaction mixture was stirred at 0 – 5 °C temperature in an ice-water bath till all the V_2O_5 dissolved and the solution became reddish-brown. It was then diluted with 110 mL of water and poured into a 500 mL beaker that was placed in an ice-water bath. To it was added a solution of 4.89 g (41.07 mmol) of potassium bromide (KBr) and 5g (13.74 mmol) of cetyltrimethylammonium bromide (CTMAB), dissolved in 150 mL of water. An amount of 25 mL of 1M sulphuric acid (H_2SO_4) was added in small portions to the above solution. Magnetic stirring was continued for another 2 h at ice-water

temperature. The product that formed was then isolated by suction filtration using Whatman 1 filter paper.



The compound was then dried in a vacuum desiccator using anhydrous calcium chloride ($CaCl_2$) as desiccant. The product was obtained as bright yellow micro-crystals. Yield of the product was 5.52 g (96 %). M.p. 87 – 88 °C.

A Typical Example of Optimization of Synthetic Protocol: In case of any synthetic methodology, catalysts as well as all other reagents are expected to be used optionally so as to reduce the burden on the eco-system.

Table 3.1. Optimization of Synthesis of **CTMATB**

CTMAB g (mmol)	V_2O_5 g (mmol)	30 % H_2O_2 mL (mmol)	KBr g (mmol)	1M H_2SO_4 mL (mmol)	yield g (%)
5 (13.74)	0.63 (3.45)	4.4 (38.63)	-	-	1.6 (23)
5 (13.74)	0.12 (0.69)	5 (44.1)	3.56 (29.97)	25 (25)	4.9 (68)
5 (13.74)	0.12 (0.69)	5 (44.1)	4.89 (41.07)	25 (25)	6.9 (96)
5 (13.74)	**0.06 (0.34)**	**5 (44.1)**	**4.89 (41.07)**	**25 (25)**	**6.9 (96)**
5 (13.74)	0.06 (0.34)	5 (44.1)	4.89 (41.07)	20 (20)	5.4 (75)
5 (13.74)	0.06 (0.34)	5 (44.1)	3.56 (29.97)	25 (25)	4.2 (59)
5 (13.74)	0.02 (0.14)	5 (44.1)	4.89 (41.07)	25 (25)	2.7 (38)

The optimization of the synthesis requires a number of reaction runs to be carried out to arrive at the optimum amount of all the reagents used. A typical exercise of

reagent optimization, with the synthesis of **CTMATB** being the reference is summarized in Table 3.1.

Thus, **the ideal mmolar stoichiometry among the different reagents used and the amount of acid (mL) recommended for the synthesis of CTMATB are as follows:**

CTMAB	V_2O_5	30% H_2O_2	KBr	1 M H_2SO_4
13.74	0.34	44.12	41.07	25

Similarly, the results of catalysts optimization cause us to recommend the following stoichiometries to be suitable for the syntheses of **TMATB**, **TEATB** and **TBATB**:

For **TMATB**:

TMAB	NH_4VO_3	30% H_2O_2	KBr	0.5 M H_2SO_4
32.47	1.6	176.47	130.25	50

TMAB	$H_2MoO_4.H_2O$	30% H_2O_2	KBr	0.8 M H_2SO_4
32.5	0.32	176.47	130.3	50

TMAC	$H_2MoO_4.H_2O$	30% H_2O_2	KBr	1 M H_2SO_4
45.5	0.44	264.91	268.91	100

For **TEATB**:

TEAB	V_2O_5	30% H_2O_2	KBr	1 M H_2SO_4
23.81	0.27	44.12	47.65	25

For **TBATB**:

TBAB	V_2O_5	30% H_2O_2	KBr	1 M H_2SO_4
15.53	0. 27	44.12	31.09	25

X-RAY STRUCTURE DETERMINATION OF TBATB[34]

Orange-red crystals of **TBATB** were obtained by slow-evaporation of a CH_3CN solution. Cell parameters were determined by a least-squares fit 25 machine centered reflections in the range $12° \leq 2\theta \geq 25°$. Data were collected at 22°C on a Siemens R3m/V diffractometer employing Mo Kα radiation (Graphite monochromator) at $\lambda = 0.71073$ Å by omega scan technique in the range $3 ° \leq \omega \geq 45°$. Two check reflections measured after each 198 reflections showed no intensity reduction. All the data were corrected for Lorentz-polarization effects and absorption. The structure was solved by Patterson method and refined by full-matrix least-squares technique using SHELXTL PLUS (VMS version).

OXIDATIVE BROMINATIONS USING TETRAMETHYLAMMONIUM TRIBROMIDE (TMATB), $(CH_3)_4NBr_3$, TETRAETHYLAMMONIUM TRIBROMIDE (TEATB), $(C_2H_5)_4NBr_3$ and CETYLTRIMETHYLAMMONIUM TRIBROMIDE (CTMATB), $(C_{16}H_{33})(CH_3)_3NBr_3$

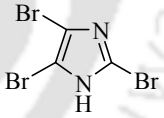
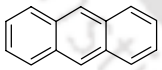
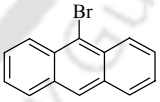
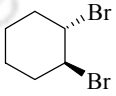
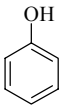
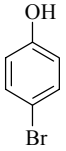
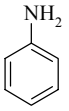
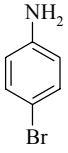
A Typical Procedure for the Oxidative Bromination of Organic Substrates using TMATB

Bromination of cyclohexene: To a stirred solution of 0.57 mL (10 mmol) of cyclohexene dissolved in 5 mL acetonitrile was added 3.45 g (11 mmol) of **TMATB** dissolved in the 15 mL of the same solvent. The reaction was stirred at room temperature and the progress of the reaction was monitored by TLC and GC till starting material could be no longer detected. The solvent was then removed *in vacuo* and the residue redissolved in ethyl acetate (20 mL). The organic layer was

first washed with 5% sodium metabisulfite solution (2x5 mL) then with water (3x5 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by column chromatography (silica gel; 100% hexane) to afford the corresponding brominated product as 1,2 dibromocyclo-hexane as a liquid, in 100% yield. (1.35 mL)

To determine the efficacy of **TMATB** as brominating agent in solution a few more reactions were conducted. The specific molar ratios of the substrates and the reagent, and the corresponding percentage yields of the products are all set out in Table 3.2.

Table 3.2. Bromination of Aromatics and Some Other Substrates by **TMATB**

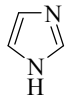
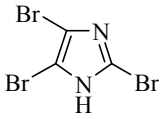
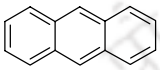
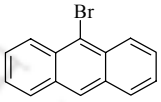
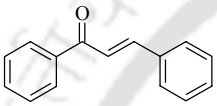
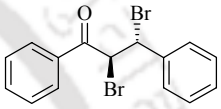
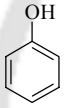
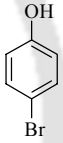
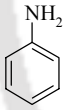
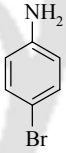
substrate	subs. : TMATB ratio	reaction conditions/ solvent	time	product	yield (%)
	1: 3	rt / CH_3CN	3.5 h		50
	1: 1	rt / CH_3CN	15 min		87
	1: 1	rt / CH_3CN	5 min		100
	1: 1	rt / CH_3CN	20 min		70
	1: 1	0-5°C / CH_3CN	5 min		67

A Typical Procedure for the Oxidative Bromination of Organic Substrates using TEATB

Bromination of anthracene: To a stirred solution of 0.5 g (2.8 mmol) of anthracene dissolved in 5 mL acetonitrile (2 mL of CH_2Cl_2 was added as co-solvent) was added 1.55 g (4.2 mmol) of **TEATB** dissolved in the 15 mL of the same solvent. The reaction was stirred at room temperature and the progress of the reaction was monitored by TLC and GC till starting material could be no longer detected. The solvent was then removed *in vacuo* and the residue redissolved in ethyl acetate (20 mL). The organic layer was first washed with 5 % sodium metabisulfite solution (2x5 mL) then with water (3x5 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by column chromatography (silica gel; 100% hexane) to afford 9-bromo anthracene in 68% yield (0.47 g). The melting point of the product was 99 – 101 ºC. (lit. m.p. 98 – 101 ºC)[35]

To determine the efficacy of **TEATB** as brominating agent in solution a few more reactions were conducted. The specific molar ratios of the substrates and the reagent, and the corresponding percentage yields of the products are all set out in Table 3.3.

Table 3.3. A Few Typical Bromination Reactions by **TEATB**

substrate	subs. : TEATB ratio	reaction conditions/ solvent	time	product	yield (%)
	1: 3	rt/ CH_3CN	4 h		40
	1: 1.5	rt/ CH_3CN	45 min		68
	1: 1	rt/ CH_3CN	5 h		55
	1: 1	rt/ CH_3CN	4.5 h		60
	1: 1	rt/ CH_3CN	3.5 h		65

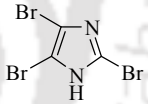
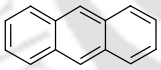
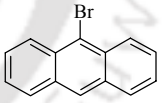
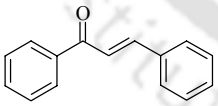
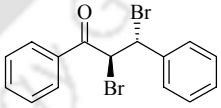
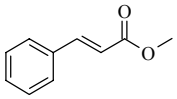
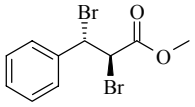
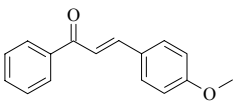
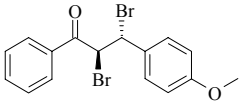
A Typical Procedure for the Oxidative Bromination of Organic Substrates using CTMATB

Bromination of chalcone: To a stirred solution of 0.21 g (1 mmol) of chalcone dissolved in 5 mL acetonitrile was added 0.524 g (1 mmol) of **CTMATB** dissolved in the 15 mL of the same solvent. The progress of the reaction was monitored by TLC and GC till starting material could be no longer detected. The solvent was then removed *in vacuo* and the residue redissolved in ethyl acetate (20 mL). The organic layer was first washed with 5 % sodium metabisulfite solution (2x5 mL) then with water (3x5 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed

in vacuo and the residue purified by column chromatography (silica gel; hexane: ethyl acetate 9:1) to afford the corresponding brominated product as 1,2 –erythro dibromochalcone in 92 % yield. (0.34 g) The melting point of the product was 159 – 160 ºC. (lit. m.p. 160 ºC)[36]

Table 3.4 gives a few cases of bromination by **CTMATB**. It may be mentioned here that the reagent has worked very well with a host of other substrates including phenol, aniline, *o*-cresol, *p*-cresol, phloroglucinol and *o*-nitroaniline as well.

Table 3.4. Some of the Bromination Reactions by **CTMATB**

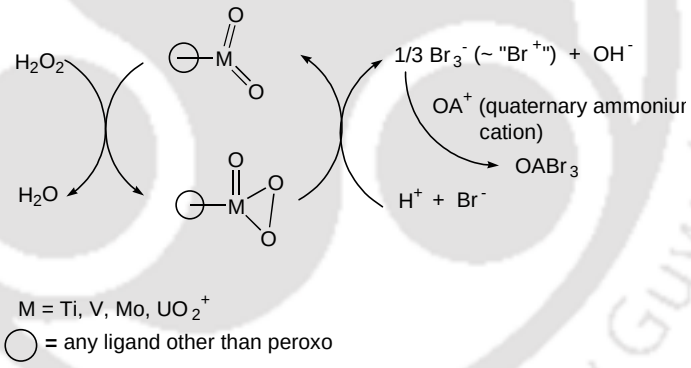
substrate	sub: CTMATB ratio	reaction conditions/ solvent	time (h)	product	yield (%)
	1: 3	rt/CH_3CN	5		55
	1: 1.2	rt/CH_3CN	4.5		87
	1: 1	rt/CH_3CN	5		92
	1: 1	reflux/ CH_3CN	4.5		78
	1: 1	rt/CH_3CN	3.5		67

RESULTS AND DISCUSSION

STRATEGY FOR THE SYNTHESIS AND ISOLATION OF THE QUATERNARY AMMONIUM TRIBROMIDES (QATBs)

Following the synthesis of a large number of a variety of peroxo-compounds of different metals including titanium, vanadium, cobalt, copper, molybdenum, zirconium, and UO_2^{2+}, for instance, in our laboratories, investigation of their reactivity profiles was initiated.[29] To begin with our focus was mainly on the oxidation of inorganic substrates. It was observed during the reactivity experimentations that many of the peroxo-complexes available in the laboratories oxidized Br^- in an acidic medium (*c.f.,* $HClO_4$, H_2SO_4). To cite a few examples, $[Ti(O_2)F_5]^{3-}$, $[VO(O_2)_2F]^{2-}$ and $[UO_2(O_2)F_2]^{2-}$ readily interacted with Br^- in an aqueous acidic medium to provide in each case an orange yellow solution with a characteristic electronic absorption at *ca.* 267 nm which has been ascertained to be due to the formation of Br_3^- in solution.[16-18] Looking back into the literature,[13] it was found that peroxo-complexes of higher valent transition metals including peroxovanadium(V) were reported to be capable of bringing about bromide oxidation in an acidic condition leading to $OBr^- \leftrightarrows Br_2 \leftrightarrows Br_3^-$. However, there was no reported evidence of salts of Br_3^- having been synthesized and isolated in the solid state from such reactions. Meanwhile, information on vanadium bromoperoxidase enzyme (VBrPO) activities started emerging suggesting that VBrPO catalyzed oxidative brominations of marine natural products apparently involving $\{Enzyme\text{-}Br\}^+$, HOBr, BrO^-, Br_2 or Br_3^- as active brominating species.[8,13,14]

Going back to the laboratory experiments referred to above on Br^- oxidation, what was observed was that tetrabutylammonium bromide, Bu_4NBr, on being reacted with peroxovanadium(V) complexes, afforded orange-yellow crystalline product in very high yield which was finally identified to be tetrabutylammonium tribromide, **TBATB**, Bu_4NBr_3.[37] Indeed this provided a lead to further our studies in this direction so that a generalization could be made. Also hoped was that there might be an emergence of some parallelism between such laboratory experiments and VBrPO enzyme catalyzed natural processes. The laboratory experiments producing Br_3^- in solution and ultimately affording solid quaternary ammonium tribromides, **QATBs** may be depicted as shown in Scheme 3.1.



Scheme 3.1. Mechanistic Pathway for QATB Synthesis

Mechanistically, for instance, VO_2^+ (of which V_2O_5 is a precursor) serves as a functional mimic of VBrPO although, unlike the enzyme, it functions in acidic conditions and at much lower turnover rates.[38] What happens in a weakly acidic condition, therefore, is that cis- VO_2^+ coordinates with one or two equivalent of H_2O_2 in solution forming $VO(O_2)^+$ and/or $VO(O_2)_2^-$ species both of which being capable of oxidizing bromide to HOBr ⇆ Br_2 ⇆ Br_3^-.[39] It has now been shown that following the protocol developed by us (*vide* Experimental), Br_3^- can be isolated in

solid state using appropriate counter cations. It may be noted that in a situation where the oxidized bromide is not isolated, it oxidizes a second equivalent of H_2O_2 to O_2.[40] Alternatively, if an appropriate organic substrate is present in the reaction solution, i.e., in the vicinity of the active brominating species within the reactive collisional limit, then the corresponding brominated product is formed, as is often the case with haloperoxidase in marine aquatic conditions.[10]

Taking cues from the successful synthesis of tetrabutylammonium tribromide (**TBATB**), Bu_4NBr_3, by a VBrPO catalytic reaction mimicking route, several other tribromides, *viz.*, tetramethylammonium tribromide (**TMATB**), $(CH_3)_4NBr_3$, tetraethylammonium tribromide (**TEATB**), $(C_2H_5)_4NBr_3$, and cetyltrimethylammonium tribromide (**CTMATB**), $(C_{16}H_{33})(CH_3)_3NBr_3$ have also been synthesized in high yields (*vide* Experimental). Indeed a successful extension of this methodology has been made to the preparation of highly crystalline product of benzyltrimethylammonium tribromide $(C_6H_5CH_2)(CH_3)_3NBr_3$, though it and its reaction profiles do not form a part of the present thesis. The successful synthesis of a number of quaternary ammonium tribromides (**QATBs**) by a single protocol makes this methodology a general one with the accompanying advantages being that the method is facile affording very high yield of the products with enhanced stability for not making use of HBr and above all the method is environmentally benign especially for not making use of Br_2 and HBr in the synthesis which are declared to be environmentally hazardous. It is also relevant to mention that the chosen cations have been used as counter cations because of their being bulky and relatively heavy which facilitates precipitation of the tribromides (i.e., **QATBs**). In addition, the

nature of the cations causes the anticipated higher solubility of such tribromides in organic solvents. Yet another property of such compounds that was considered to be of value is their stability. All these tribromides are stable up to their corresponding melting points with **TEATB**, **TBATB** and **CTMATB** being stable even up to *ca.* 200°C. One of the major implications of this property is that the tribromides may be very useful for the appropriate solvent-free organic transformations at relatively higher temperatures as well. Some work in this direction, addressing bromination of aromatics, has already been initiated by our collaborators, and the results that have been obtained so far are very encouraging. Solvent-free reactions of organic substrates are extremely important for both laboratory preparations as well as commercial scale manufactures because they are not only economic but also clean and ecologically non-hostile or far less hostile compared to their solution reaction counterpart.

Significantly, the existence of Br_3^- in solution can be monitored by its characteristic absorption spectrum showing a strong absorption at *ca.* 268 nm (ε greater than 50,000 [usually 52,000] $M^{-1}cm^{-1}$) with a shoulder at 400 nm (ε ≈ 145 $M^{-1}cm^{-1}$).[16,17] In vanadium(V) catalyzed reactions, the involvement of peroxovanadium(V) intermediate as an active oxidant can be ascertained from the observance of the peroxo-vanadium charge transfer (CT) band at 430 nm (ε ≈ 300 $M^{-1}cm^{-1}$) in aqueous vanadium(V) – H_2O_2 solution.[37]

Thus, the synthesis of the tribromides described herein not only provides an easy access to such compounds but also evidences the formation of Br_3^- in solution being catalyzed by peroxo-metal intermediates. However, although it is certain that

Br_3^- is an oxidized product of Br^- under VBrPO mimicking condition, formation of other oxidized bromide species like OBr^- or Br_2 are not ruled out.

CHARACTERIZATION AND STRUCTURAL EVALUATION

The compounds **TMATB**, **TEATB**, **TBATB** and **CTMATB** are all bright yellow to orange in colour and crystalline in nature. Recrystallization from acetonitrile gives deep orange crystals. X-ray quality crystals can also be obtained in this way (*c.f.* X-ray structure of **TBATB**). (*vide infra)*. Each of the four compounds has a sharp melting point as reported herein, which was corroborated by DSC experiments (Figures 3.1 – 3.4), and all of them have a moderate to high solubility in the common organic solvents. Acetonitrile can be solvent for reaction studies because of environmental acceptability. The tribromides synthesized by the present protocol have all a very long shelf life. Stored in sample vials, they stay stable for months. Their stability can be ascertained by the determination of bromine contents periodically and recording melting points from time to time.

Solution electrical Conductance Measurements

The solution electrical conductance (Λ_M) of the four tribromides recorded at room temperature in 10^{-3} M acetonitrile solutions lie in the range 115-165 $\Omega^{-1}cm^2mol^{-1}$. The conductance values (Table 3.5) are in order suggesting that the compounds are 1 : 1 electrolytic in nature, in total agreement with their formulae.[41] Importantly, recording of Λ_M values against time over a period of several days did not show any significant change thereby attesting to their stability in solution. This

knowledge is important especially in the context of any solution state investigations including reactivity studies in solution.

Table 3.5. Melting points, Analytical Data and Molar Conductance Values of **TMATB**, **TEATB**, **TBATB** and **CTMATB**

compound (QATB)	m.p. (°C)	% found (% calcd)				conductance (10^{-3} M) ($\Omega^{-1}cm^2mol^{-1}$)
		C	H	N	Br	
TMATB ($C_4H_{12}NBr_3$)	117-118	15.29 (15.31)	3.86 (3.85)	4.45 (4.46)	76.4 (76.38)	165
TEATB ($C_8H_{20}NBr_3$)	85-86	25.99 (25.97)	5.82 (5.45)	3.67 (3.79)	64.52 (64.79)	115
TBATB ($C_{16}H_{36}NBr_3$)	75	39.41 (39.86)	8.28 (7.52)	2.78 (2.90)	49.53 (49.71)	155
CTMATB ($C_{19}H_{42}NBr_3$)	87-88	40.99 (43.53)	7.91 (8.07)	2.74 (2.67)	48.36 (45.72)	162

Electronic Spectroscopic Studies

As already mentioned in passing, solution electronic spectroscopy seems to be an extremely important technique for characterization of tribromides as Br_3^- in solution bears characteristic signatures at *ca.* 265 nm with a shoulder at *ca.* 385 nm due to the transitions σ - σ^* and π - π^*, respectively.[16,17] The σ - σ^* and π - π^* transitions for the tribromides under discussion gave values in the range 267 – 269 nm and 380 – 400 nm, (Figures 3.5 – 3.8, Table 3.6) respectively, thereby conforming to the identity of the compounds as tribromides.

Infrared Spectroscopic Studies

Similarly, the vibrational spectroscopy is also a very important technique for characterization of tribromides. For a linear tribromide (Br_3^-), three vibrational modes, ν_{sym} (ν_1), ν_{asym} (ν_3) and bending (ν_2) are expected in the far-IR region.[42] Of the three modes ν_1 and ν_3 occur at *ca.* 165 cm^{-1} and *ca.* 195 cm^{-1}, respectively, while the bending mode ν_2 generally appears at a far low value of *ca.* 50 cm^{-1}. In the present vibrational spectroscopic experiments ν_1 and ν_3 have been observed in the range 145 – 172 cm^{-1} and 185 – 192 cm^{-1} in complete agreement with those expected for a linear Br_3^- species. (Figures 3.9 – 3.12, Table 3.6) Unfortunately, owing to the instrumental limitations attempt to detect the ν_2 mode (at *ca.* 50 cm^{-1}) was not attempted. Going by the results described above, we tend to believe that the tribromide (Br_3^-) ions in the quaternary ammonium tribromides reported herein are linear.

Table 3.6. Structurally Significant IR and Electronic Spectral Bands of **TMATB**, **TEATB**, **TBATB** and **CTMATB**

compound (QATB)	IR		Uv-vis	
	ν (cm^{-1})	assignment	λ (nm) (ε, $M^{-1}cm^{-1}$)	assignment
TMATB ($C_4H_{12}NBr_3$)	146(s) 188(s)	ν_{sym} Br-Br, ν_1 ν_{asym} Br-Br, ν_3	269 (51000) 380 (149)	$\sigma - \sigma^*$ $\pi - \pi^*$
TEATB ($C_8H_{20}NBr_3$)	162(s) 192(s)	ν_{sym} Br-Br, ν_1 ν_{asym} Br-Br, ν_3	269 (49500) 390 (152)	$\sigma - \sigma^*$ $\pi - \pi^*$
TBATB ($C_{16}H_{36}NBr_3$)	171(s) 191(s)	ν_{sym} Br-Br, ν_1 ν_{asym} Br-Br, ν_3	267 (52000) 400 (150)	$\sigma - \sigma^*$ $\pi - \pi^*$
CTMATB ($C_{19}H_{42}NBr_3$)	152(s) 203(s)	ν_{sym} Br-Br, ν_1 ν_{asym} Br-Br, ν_3	269 (49000) 385 (150)	$\sigma - \sigma^*$ $\pi - \pi^*$

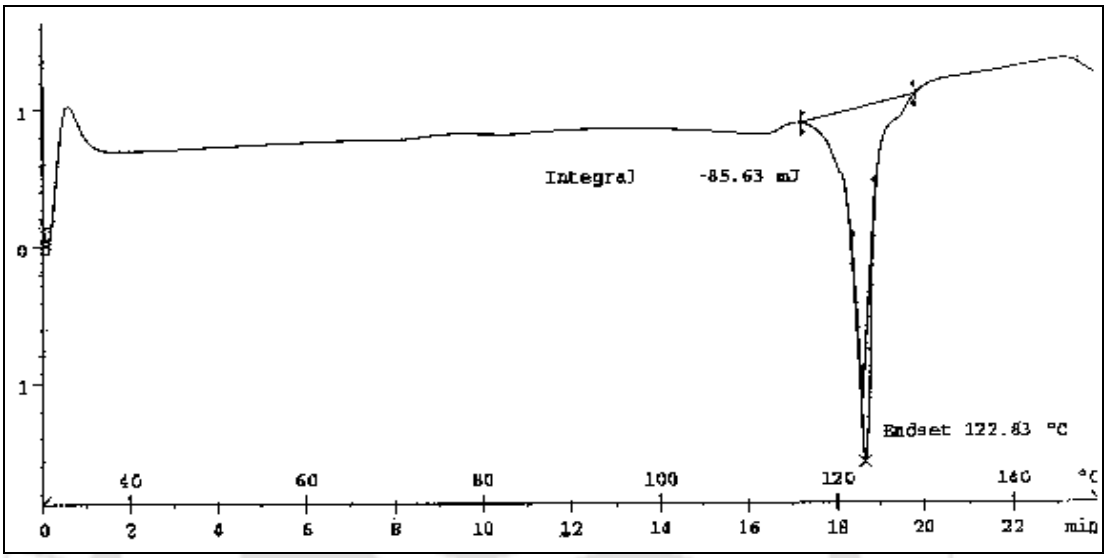


Figure 3.1 DSC curve of **TMATB**

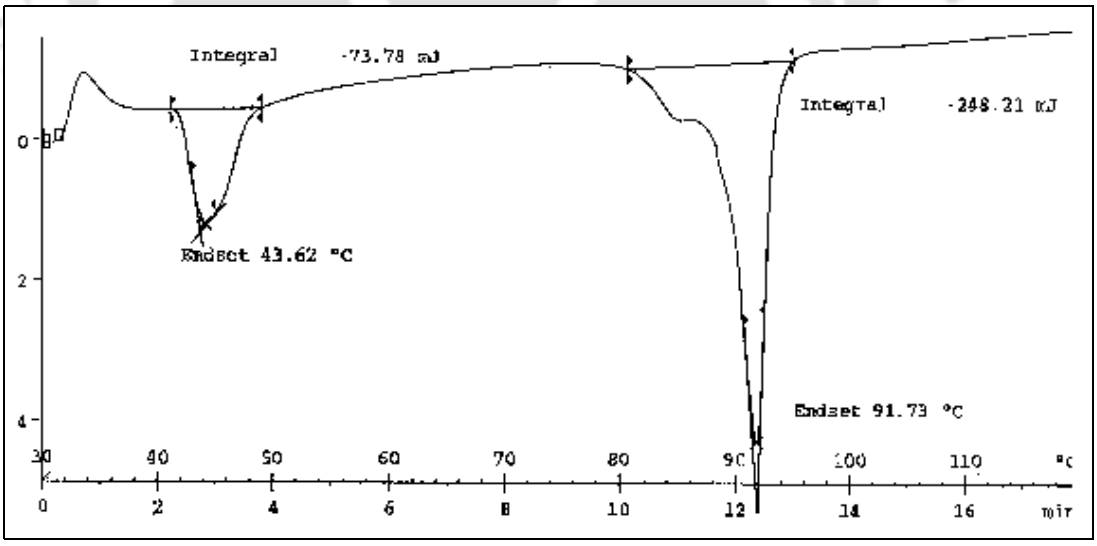


Figure 3.2 DSC curve of **TEATB**

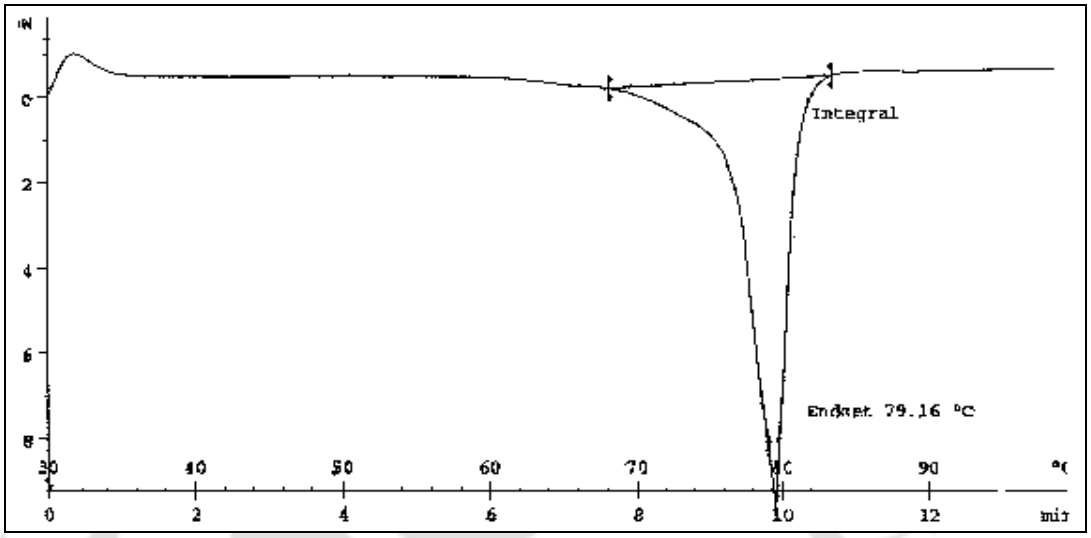


Figure 3.3 DSC curve of **TBATB**

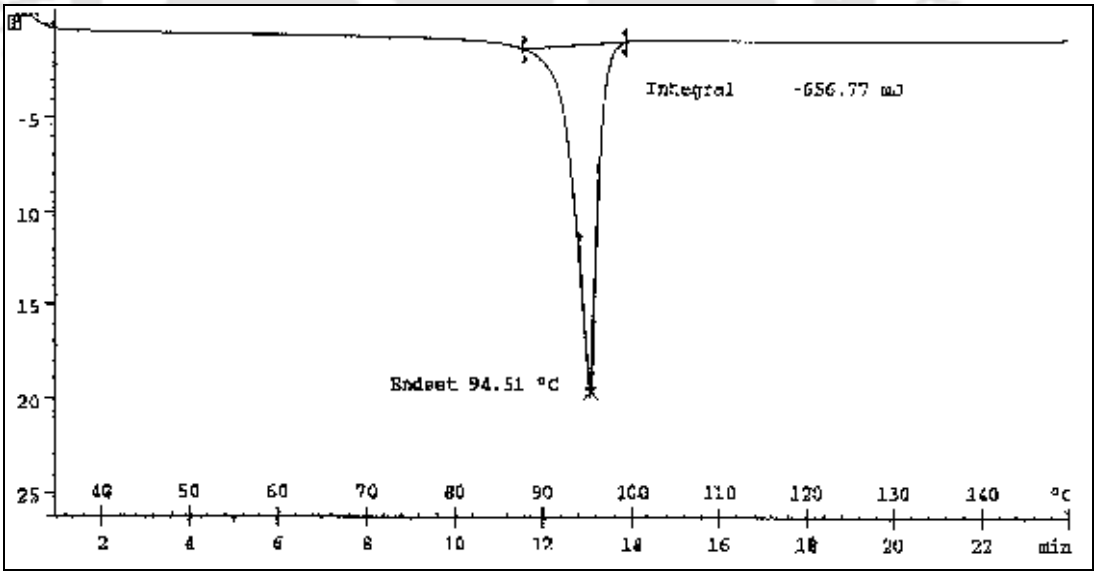


Figure 3.4 DSC curve of **CTMATB**

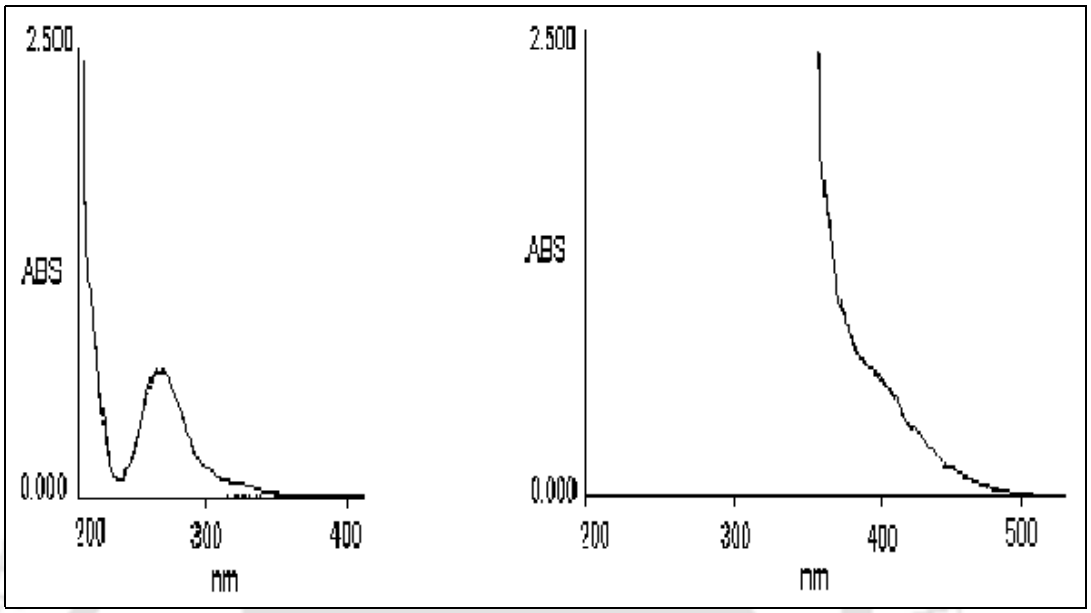


Figure 3.5 Electronic spectrum of **TMATB**

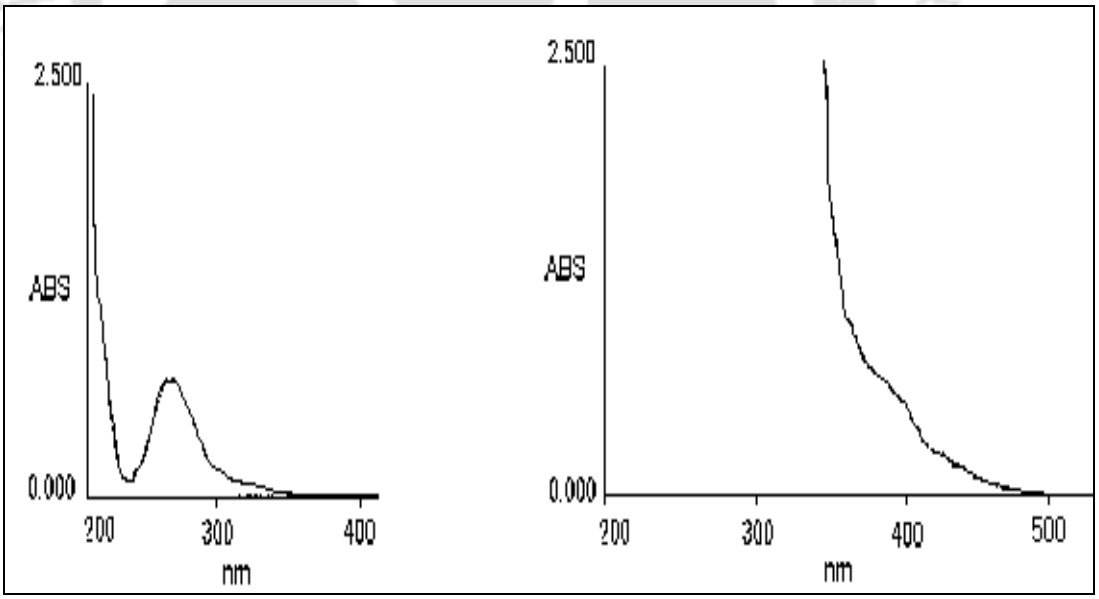


Figure 3.6 Electronic spectrum of **TEATB**

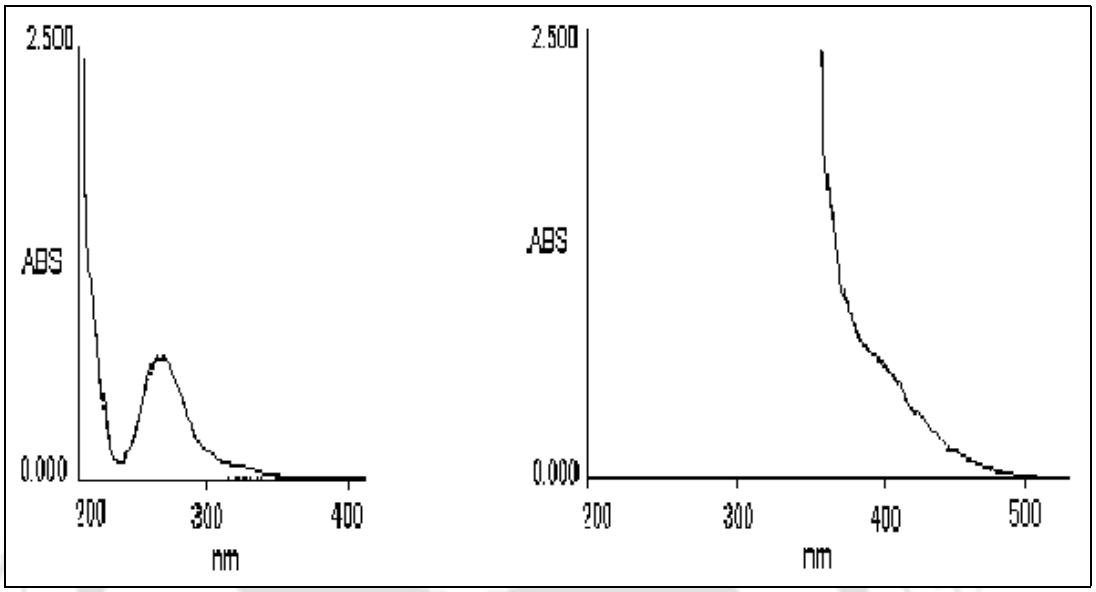


Figure 3.7 Electronic spectrum of **TBATB**

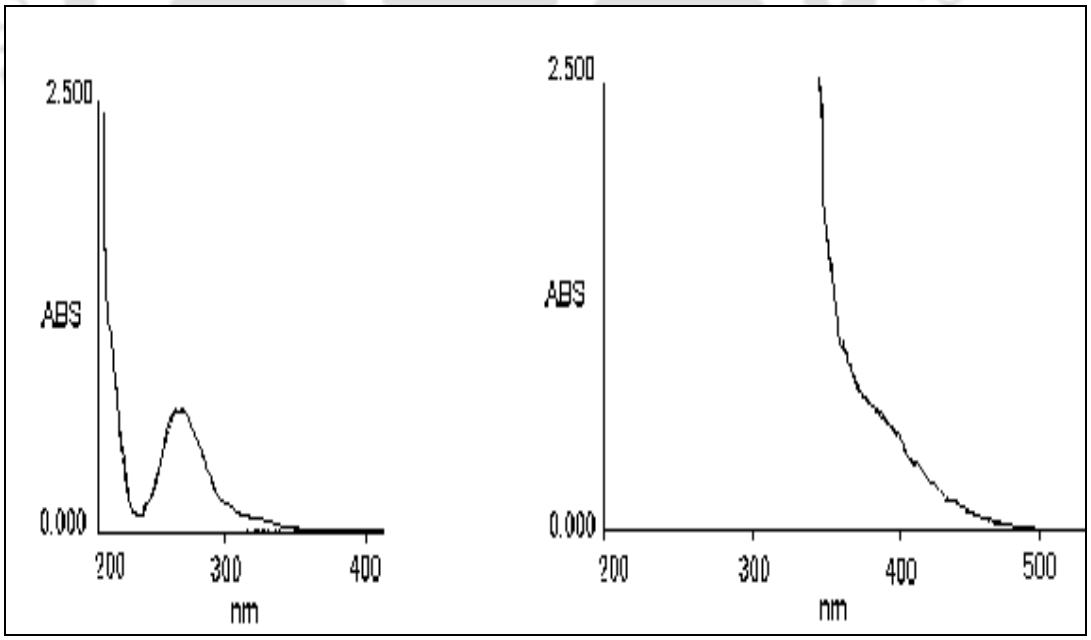


Figure 3.8 Electronic spectrum of **CTMATB**

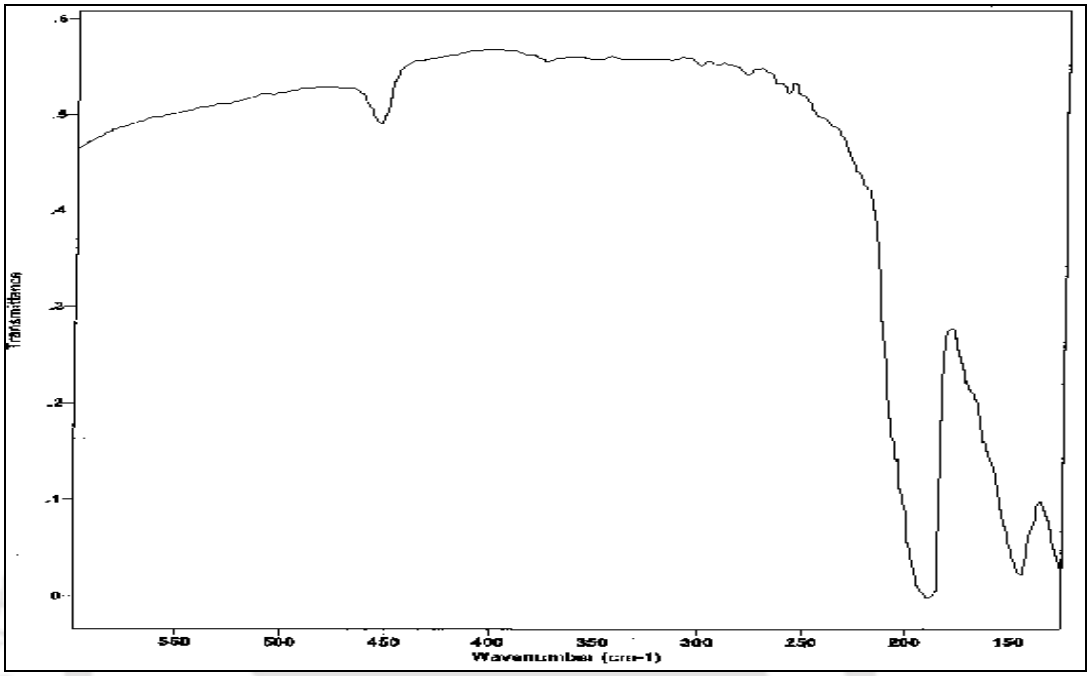


Figure 3.9 Far IR spectrum of **TMATB**

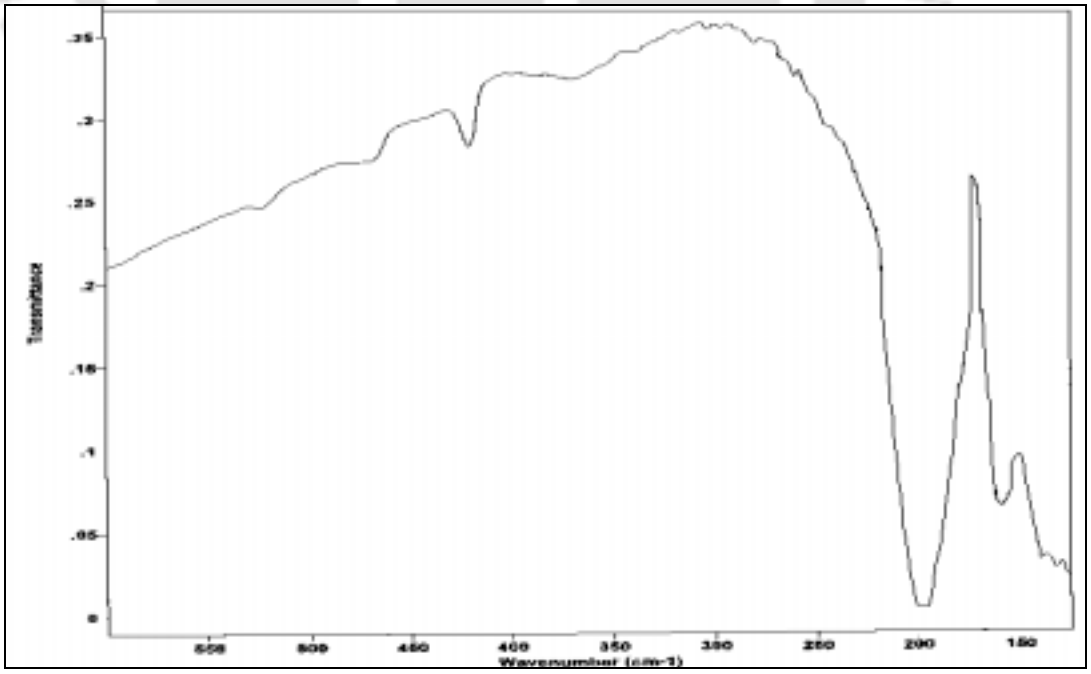


Figure 3.10 Far IR spectrum of **TEATB**

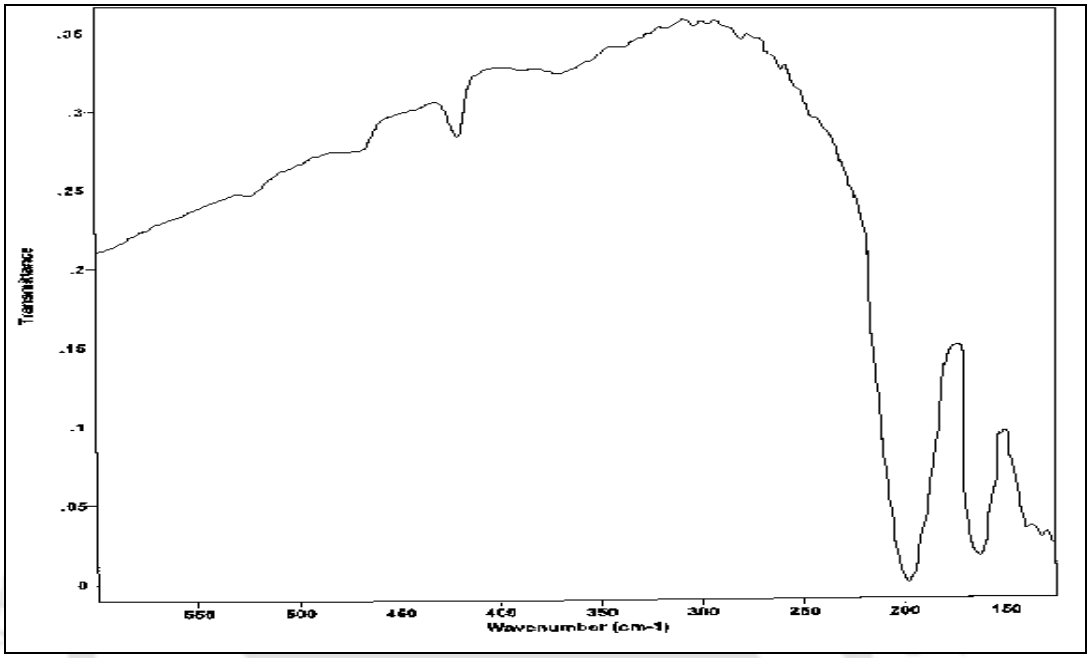


Figure 3.11 Far IR spectrum of **TBATB**

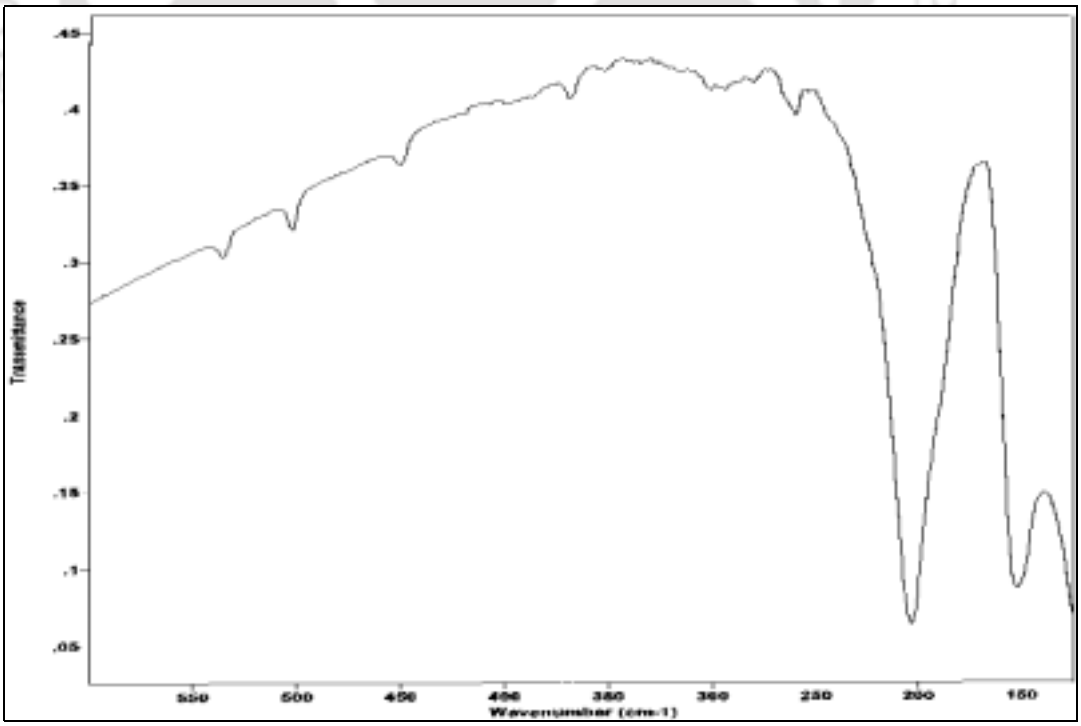


Figure 3.12 Far IR spectrum of **CTMATB**

Most significant in the context of structural evaluation is the X-ray crystal structure of tetrabutylammonium tribromide (**TBATB**), $(C_4H_9)_4NBr_3$, (Figure 3.13) as determined in our laboratory a couple of years ago.[34]

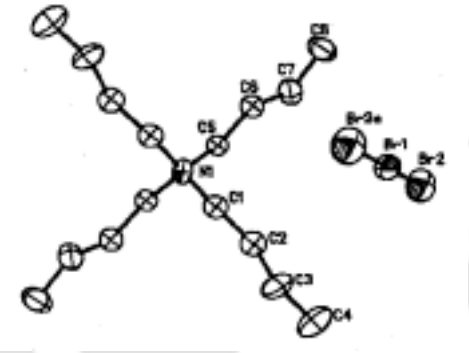


Figure 3.13 ORTEP Drawing of TBATB showing the Thermal Ellipsoids and Atomic Numbering Scheme. Hydrogen atoms are omitted for clarity

BROMINATION OF SELECTED ORGANIC SUBSTRATES BY TMATB, TEATB AND CTMATB. A COMMENT ON THEIR BROMINATION PROFILE.

Apart from their biomimetic synthesis (*c.f.* VBrPO activity), followed by ascertaining their identity, a perusal of the chemical composition especially focusing on the presence of tribromide (Br_3^-) (Figure 3.13) suggests that these compounds may be regarded as store-houses of Br_2. Infact, thermogravimetric (TGs) experiments indicated a facile loss of bromine from each of the compounds. These parameters in combination with their solubility in a number of organic solvents render them suitable as appropriate stoichiometric brominating agents.

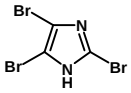
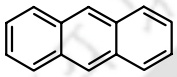
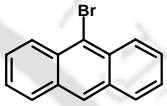
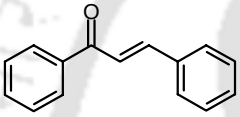
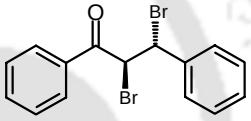
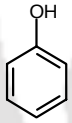
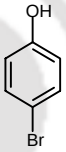
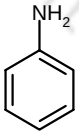
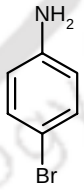
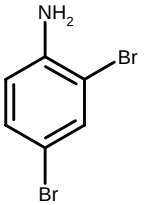
Incidentally, there are some literature reports of tribromides having been used as brominating agents. Unfortunately however, these reagents were previously not too popular. The reason for this we presume was the literature method of preparation

of these reagents which used elemental bromine and HBr, which though cheap are environmentally hazardous, whereas the present method of synthesis (*vide* Experimental) is benign. Having achieved success in the synthesis of the reagents by the new methodology, the mission would be complete if their oxidative bromination profiles were found to be satisfactory.

In order to test their efficacy, the reagents were applied to a number of chosen substrates as summarized in Table 3.7. With a view to making a comprehensive comparison, a couple of reactions reported by other co-workers were cited in Table 3.7.

It may be pertinent to mention that the substrates chosen were not simply "off the shelf" type but there was a rationale behind their selection. For instance, the substrates like phenol and aniline were chosen because it is acknowledged that most aromatic and heteroaromatic parent bromometabolites are phenols, aniline and their derivatives.[44] Again, the selection of anthracene went in its favor because among many other implications, 9-bromoanthracene also allows metal exchange reactions to be possible leading to the synthesis of compounds such as 9-vinyl anthracene, an important precursor in polymerization reactions. It is evident from literature that bromination of imidazoles is not always an easy task. In addition, brominated imidazoles have some catalytic activity and are believed to be capable of reactivating phosphorylated acetylcholinesterase.[45] Similarly, chalcones represent yet another class of substrates having biochemical relevance for they important precursors in flavonoid synthesis.[46]

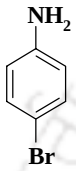
Table 3.7. A Comparative Study of the 4 Brominating Agents

substrate	reagent	reagent: substrate	product	yield (%)
	**TMATB** **TEATB** **TBATB*** **CTMATB**	**1:3** **1:3** **1:3** **1:3**		**50** **40** **68** **55**
	**TMATB** **TEATB** **TBATB*** **CTMATB**	**1:1** **1:1** **1:1** **1:1**		**87** **68** **70** **87**
	**TMATB** **TEATB** **TBATB*** **CTMATB**	**1:1** **1:1** **1:1** **1:1**		**-** **55** **65** **92**
	**TMATB** **TEATB** **TBATB*** **CTMATB****	**1:1** **1:1** **1:1** **1:1**		**70** **60** **60** **70**
	**TMATB** **TEATB** **TBATB***	**1:1** **1:1** **1:1**		**67** **65** **60**
	CTMATB**	**1:1**		**65**

* Examples have been drawn from ref. 37. ** Examples have been drawn from ref. 43.

CHARACTERIZATION OF THE BROMINATED COMPOUNDS

The brominated organic compounds were characterized by IR and ^{1}H NMR spectral techniques (Figures 3.14 to 3.29), along with melting point measurements wherever possible.

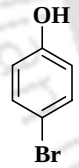


Name 4-Bromoaniline

M.p. 62-64 °C

IR (KBr): 3485, 3388, 2931, 2872, 1628, 1500, 1477, 1385, 1300, 1192, 1063, 840, 835, 623, 521 cm^{-1}

^{1}H NMR (90 MHz, $CDCl_3$) δ 7.21 (2H, d, Ar*H*), 6.54 (2H, d, Ar*H*), 3.64 (2H, brs, ArN*H*$_2$)

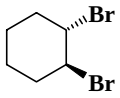


Name 4-Bromophenol

M.p. 64-68 °C

IR (KBr): 3364, 2932, 2855, 1596, 1491, 1443, 1251, 1237, 835, 612, 508 cm^{-1}

^{1}H NMR (90 MHz, $CDCl_3$) δ 7.32 (2H, d, Ar*H*), 6.71 (2H, d, Ar*H*), 5.21 (1H, s, ArO*H*)

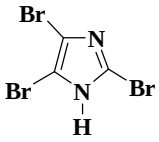


Name 1,2-Dibromocyclohexane

M.p. oily product

IR (Neat): 2942, 2871, 1456, 1445, 1182, 1000, 972, 906, 863, 818, 698, 683, 664, 553 cm^{-1}

^{1}H NMR (90 MHz, $CDCl_3$): δ 1.52 (2H, m, -C*H*$_2$-), 1.85 (4H, m, 2 x -C*H*$_2$-), 2.46 (2H, m, -C*H*$_2$-), 4.45 (2H, m, -C*H*$_2$-)

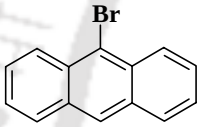


Name 2, 4, 5 - Tribromoimidazole

M.p. 221 ^{o}C (dec.)

IR (KBr): 2931, 2853, 1532, 1463, 1398, 1305, 1200,1185, 1005, 980, 832, 665, 524 cm^{-1}

MS m/z 304 (M^{+})

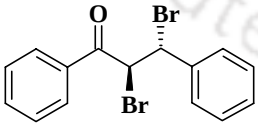


Name 9-Bromoanthracene

M.p. 99 - 101 ^{o}C

IR (KBr): 2928, 2855, 1624, 1460,1380, 1311, 1264, 955, 927, 880, 845, 768, 729, 536 cm^{-1}

^{1}H NMR (90 MHz, $CDCl_3$): δ 7.46, (2H, t, Ar*H*), 7.54 (2H, t, Ar*H*), 7.87 (2H, d, Ar*H*)

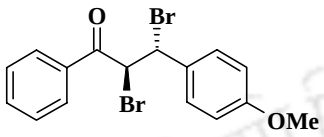


Name 2, 3-Dibromo-1, 3-diphenyl-propan-1-one

M.p. 159 - 160 ^{o}C

IR (KBr): 2920, 2865, 1681, 1600, 1460, 1400, 1380, 1276 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (d, 1H, ArC*H*)-, 5.61 (d, 1H, ArCOC*H*-), 7.0 - 7.9 (m, 10H, Ar*H*)

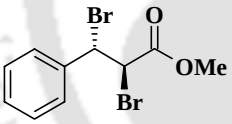


Name 2, 3- Dibromo-3(4-methoxy-phenyl)-1-phenyl-propan-1-one

M.p. liq. product

IR (KBr): 3445, 2929, 2832, 1676, 1606, 1512, 1446, 1248, 1175, 1048, 840, 820, 690 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (m, 2H, Ar*H*), 7.46 (m, 5H, Ar*H*), 6.86 (m, 2H, Ar*H*), 5.28 (d, 1H, -C*H*Br(ArH)-), 5.20 (d, 1H, -C*H*Br(CO)-), 3.8 (s, 3H, -OCH_3)



Name 2, 3- Dibromo-3-phenyl-propionic acid methyl ester

M.p. 118 °C

IR (KBr): 3033, 2928, 1767, 1721, 1639, 1460, 1440, 1320, 1285, 1174 cm^{-1}

^{1}H NMR (90 MHz, $CDCl_3$) δ 7.6 (m, 5H, Ar*H*), 5.5 (d, 1H, Ar-C*H*-), 5.0 (d, 1H, ArCHC*H*CO-), 4.0 (s, 3H, -OCH_3)

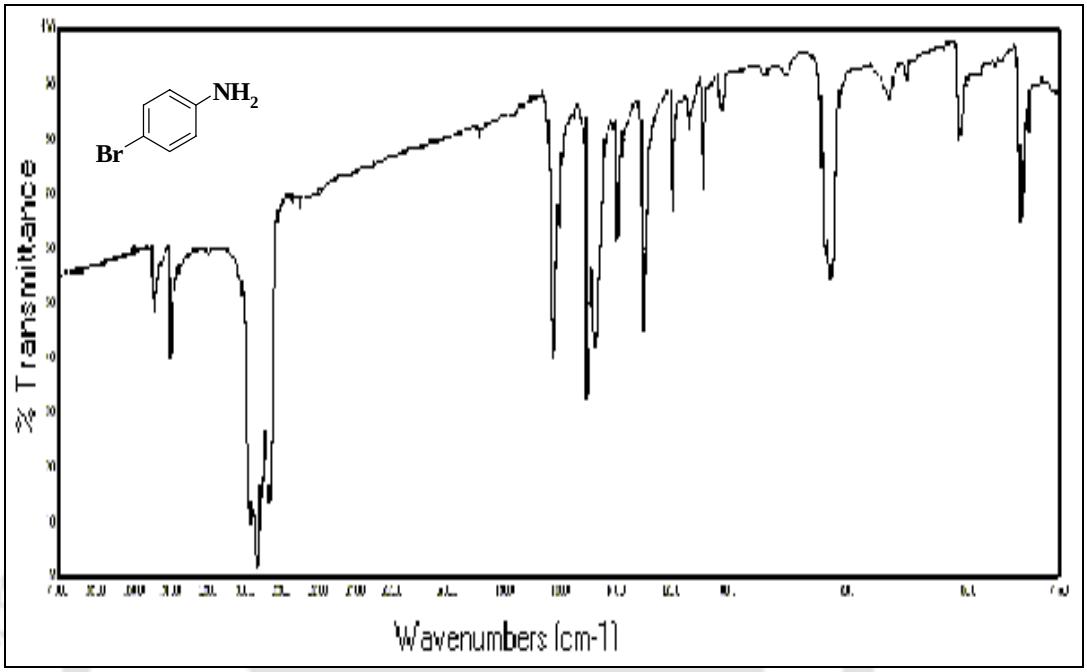


Figure 3.14. IR spectrum of **4-Bromoaniline**

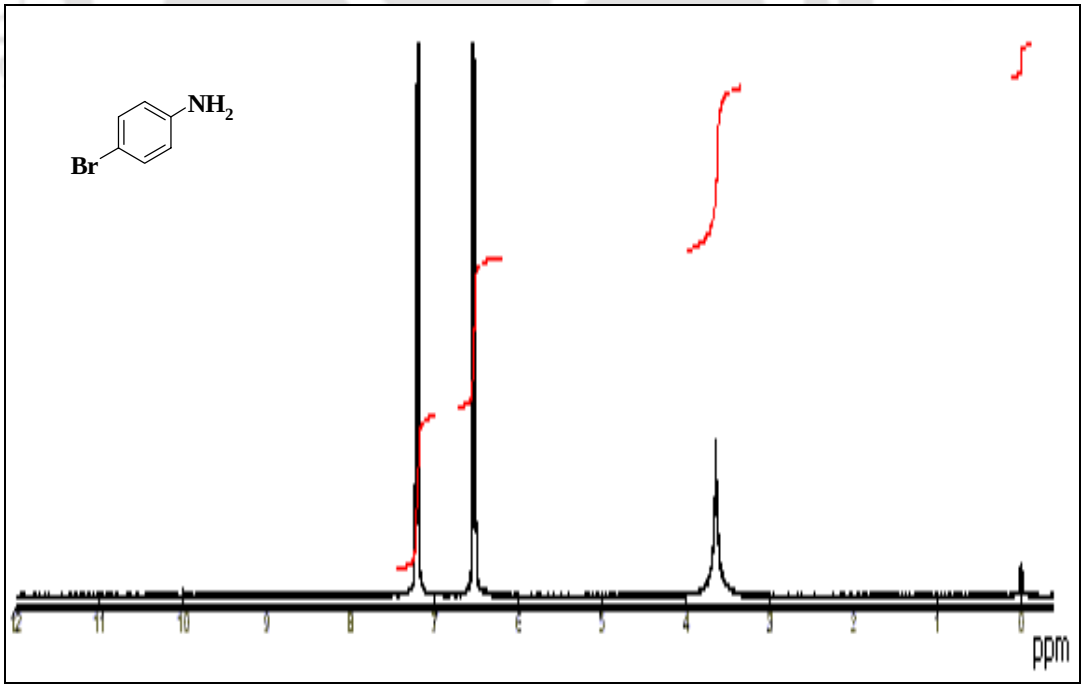


Figure 3.15. ^{1}H NMR spectrum of **4-Bromoaniline**

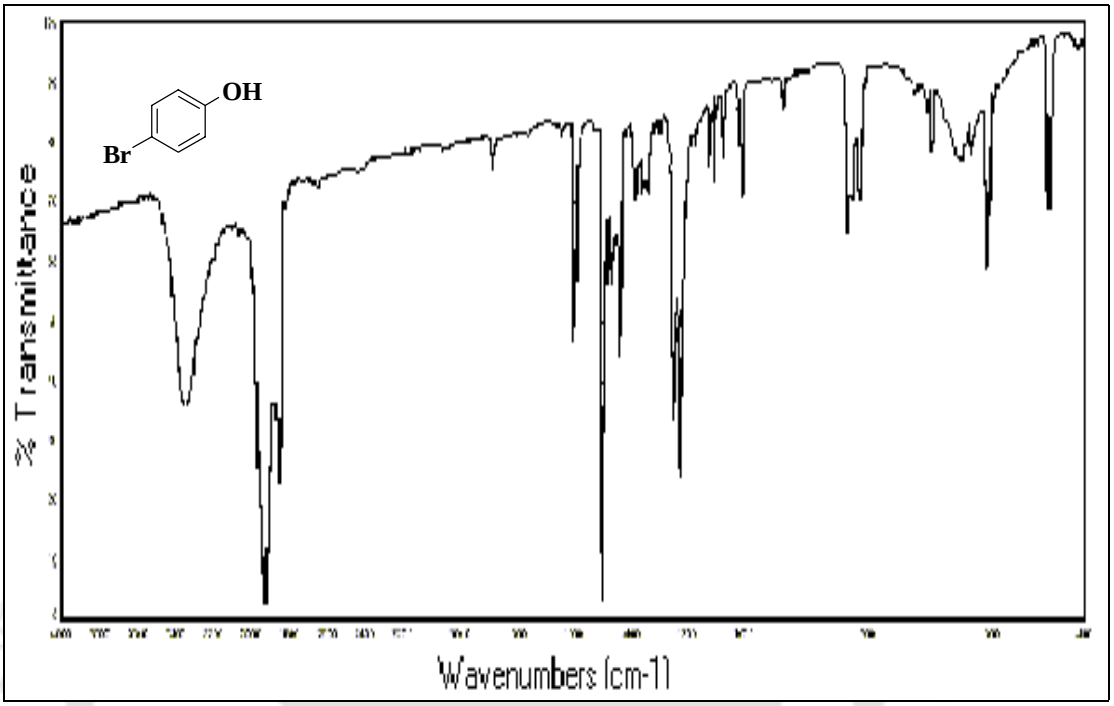


Figure 3.16. IR spectrum of **4-Bromophenol**

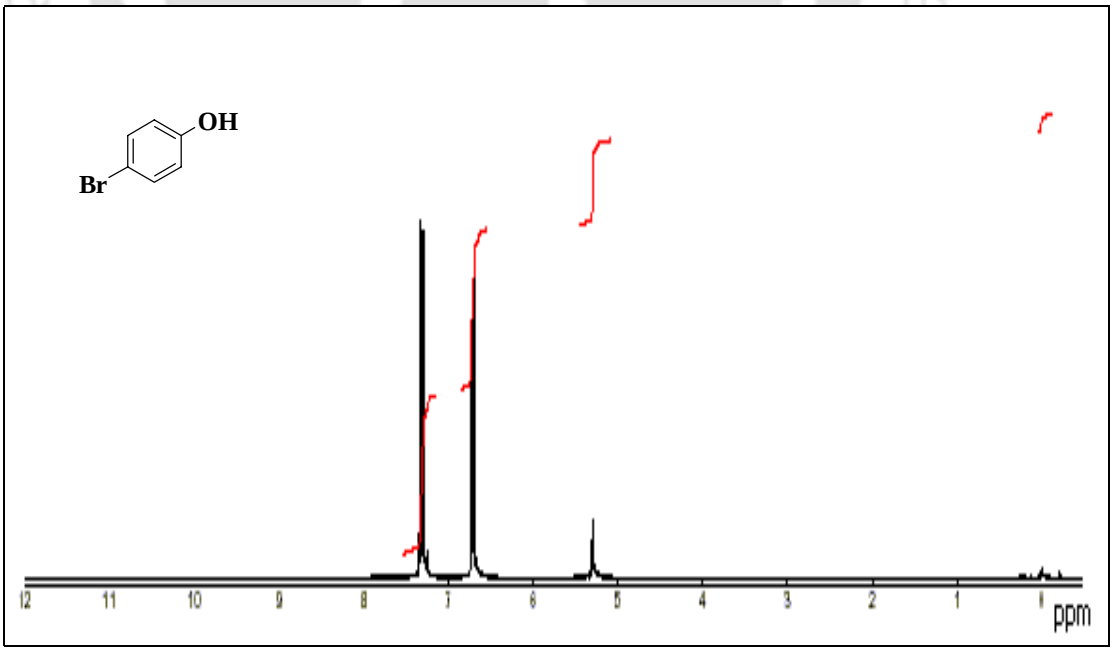


Figure 3.17. ^{1}H NMR spectrum of **4-Bromophenol**

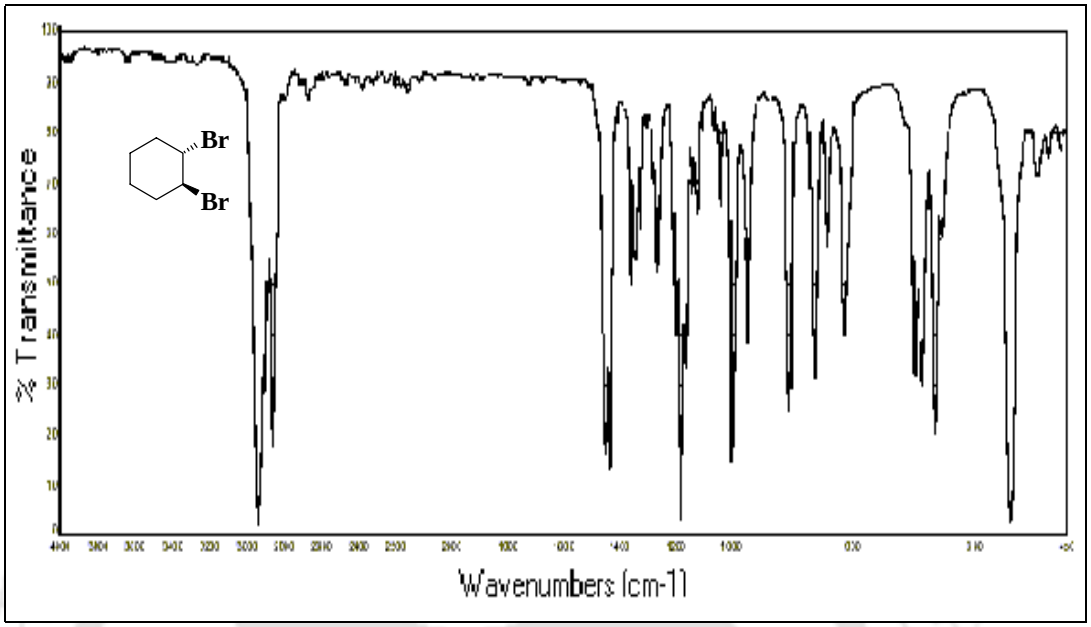


Figure 3.18. IR spectrum of **1,2-Dibromocyclohexane**

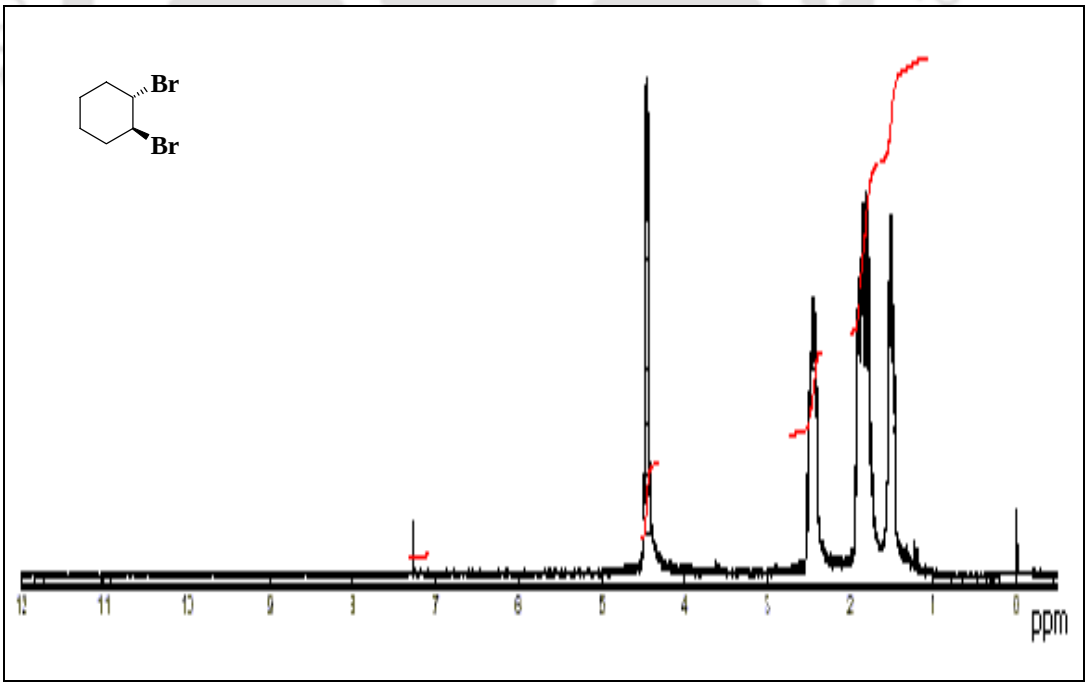


Figure 3.19. ^{1}H NMR spectrum of **1,2-Dibromocyclohexane**

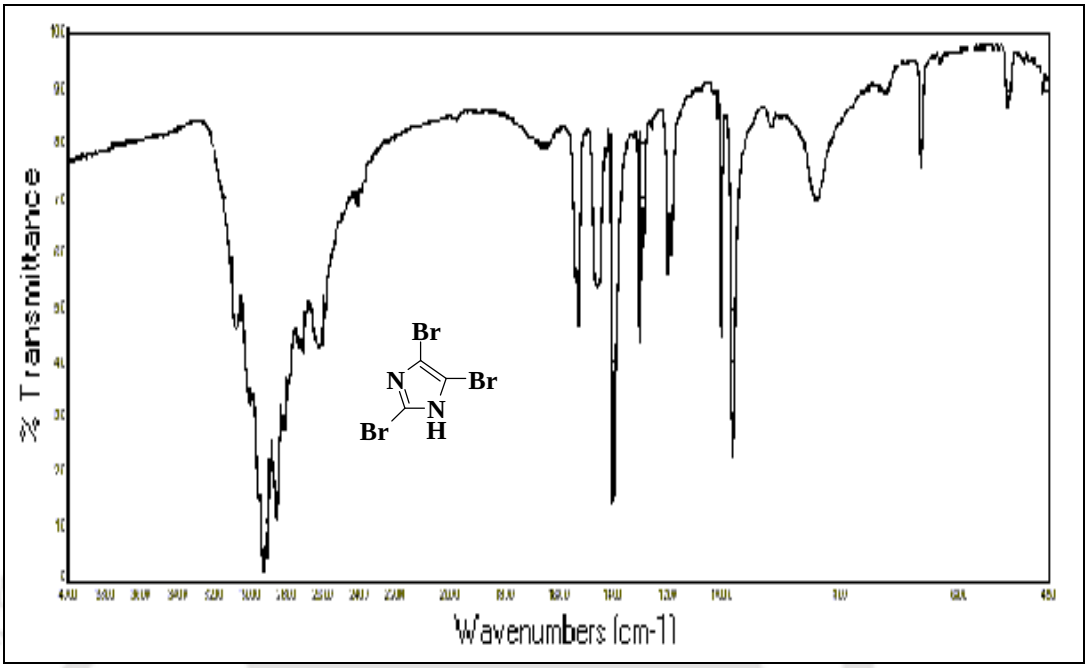


Figure 3.20. IR spectrum of **2,4,5-Tribromoimidazole**

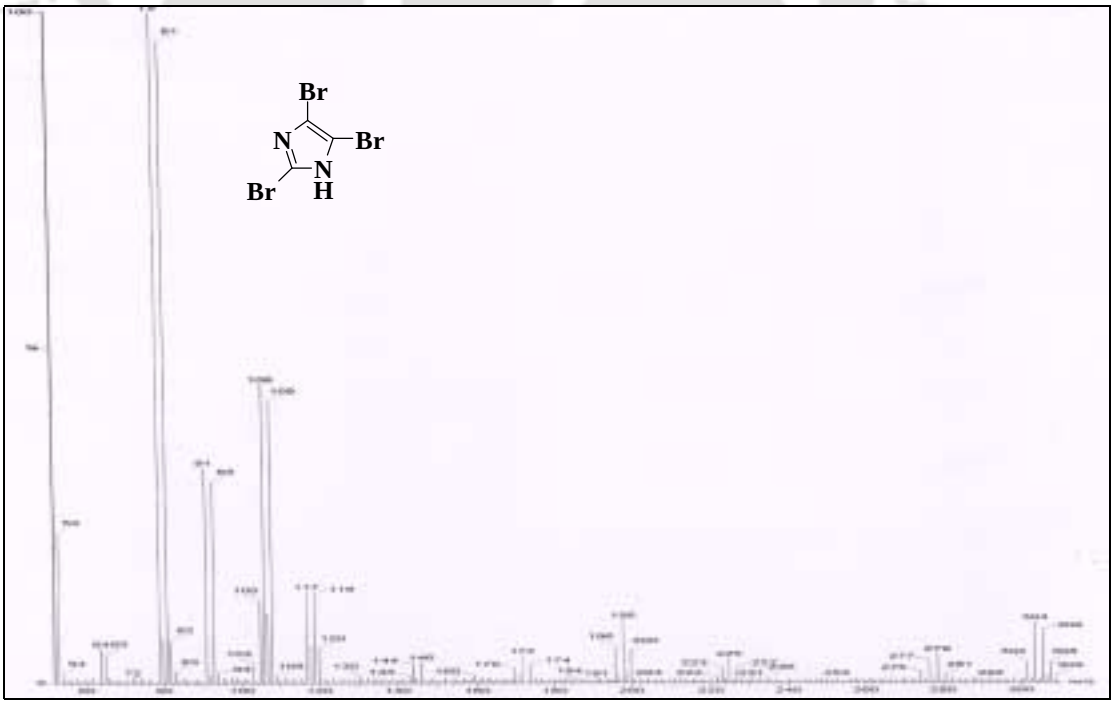


Figure 3.21. Mass spectrum of **2,4,5-Tribromoimidazole**

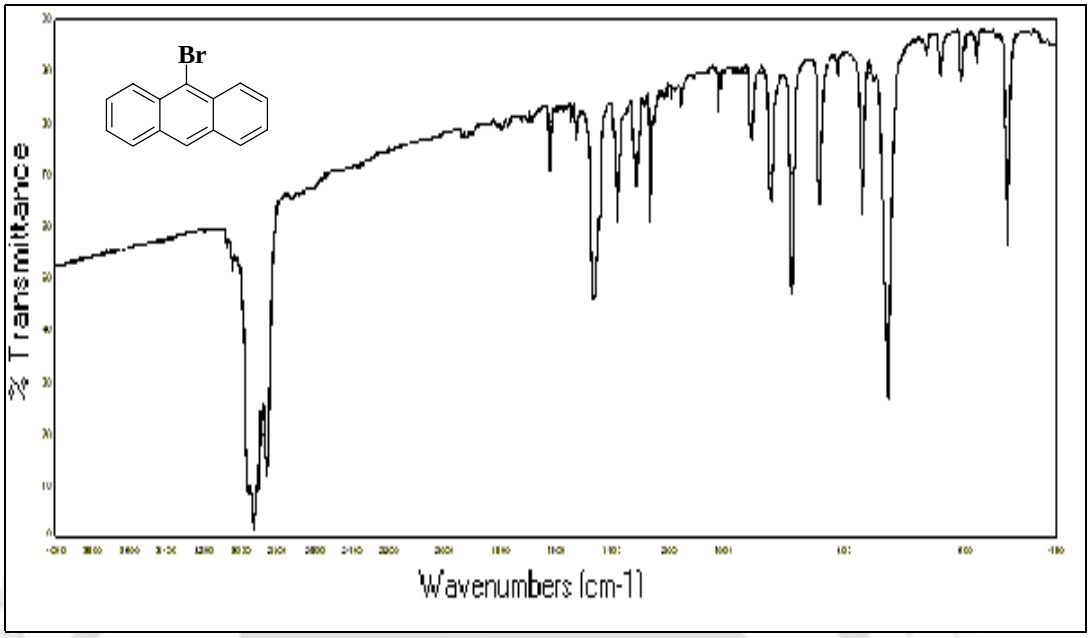


Figure 3.22. IR spectrum of **9-Bromoanthracene**

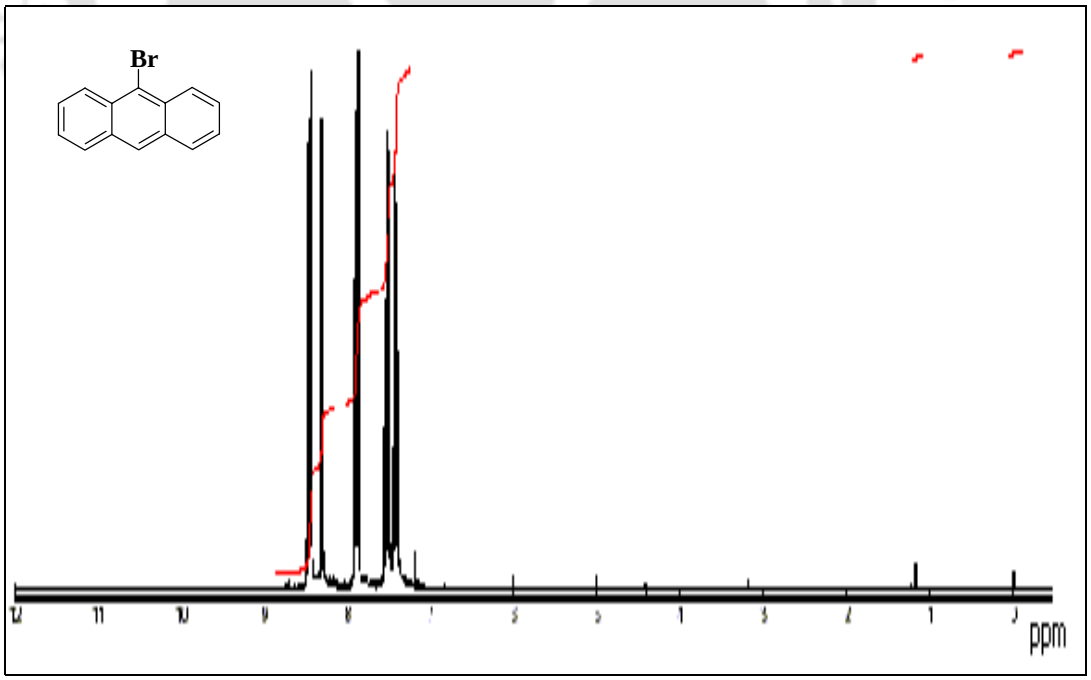


Figure 3.23. ^{1}H NMR spectrum of **9-Bromoanthracene**

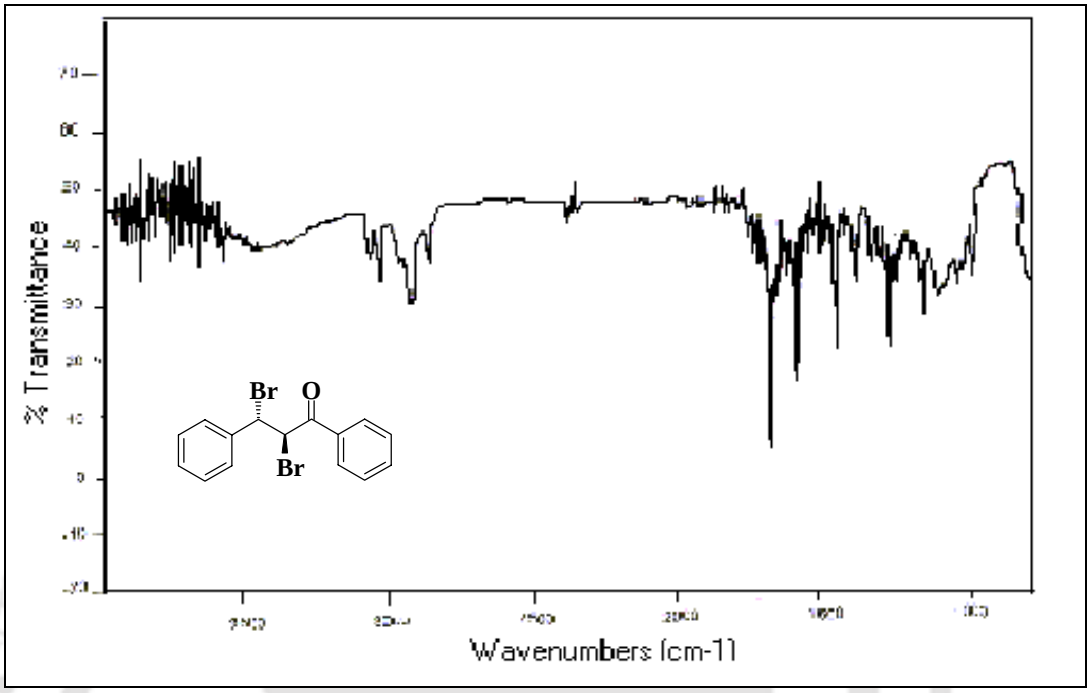


Figure 3.24. IR spectrum of **2,3-Dibromo-1,3-diphenyl-propan-1-one**

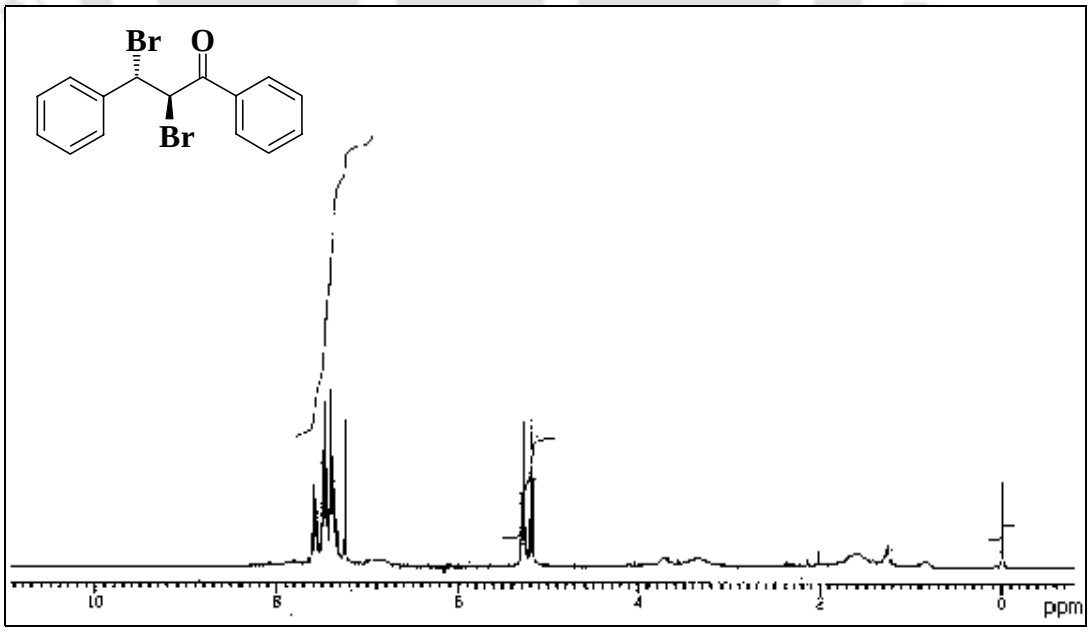


Figure 3.25. ^{1}H NMR spectrum of **2,3-Dibromo-1,3-diphenyl-propan-1-one**

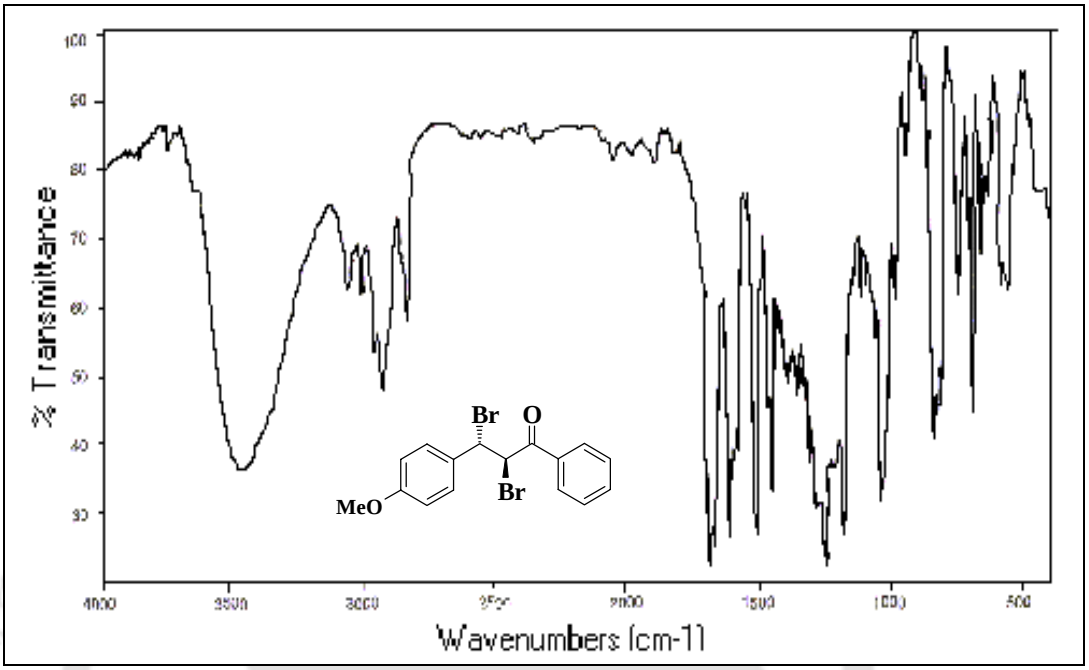


Figure 3.26. IR spectrum of **2,3-Dibromo-3(4-methoxy-phenyl)-1-phenyl-propan-1-one**

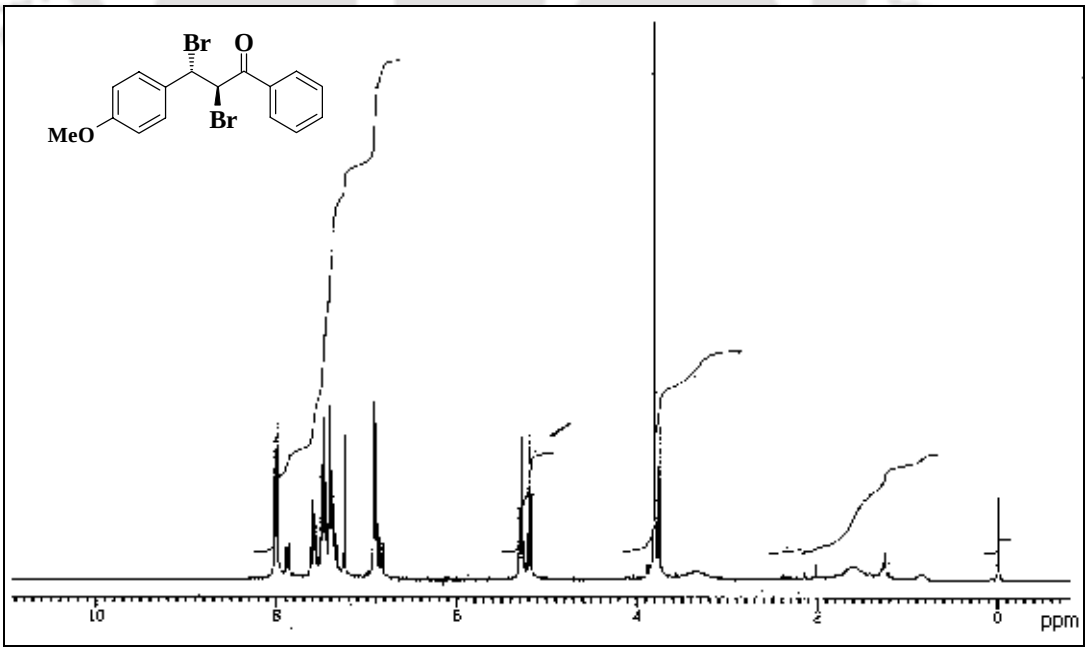


Figure 3.27. ^{1}**H** NMR spectrum of **2,3-Dibromo-3(4-methoxy-phenyl)-1-phenyl-propan-1-one**

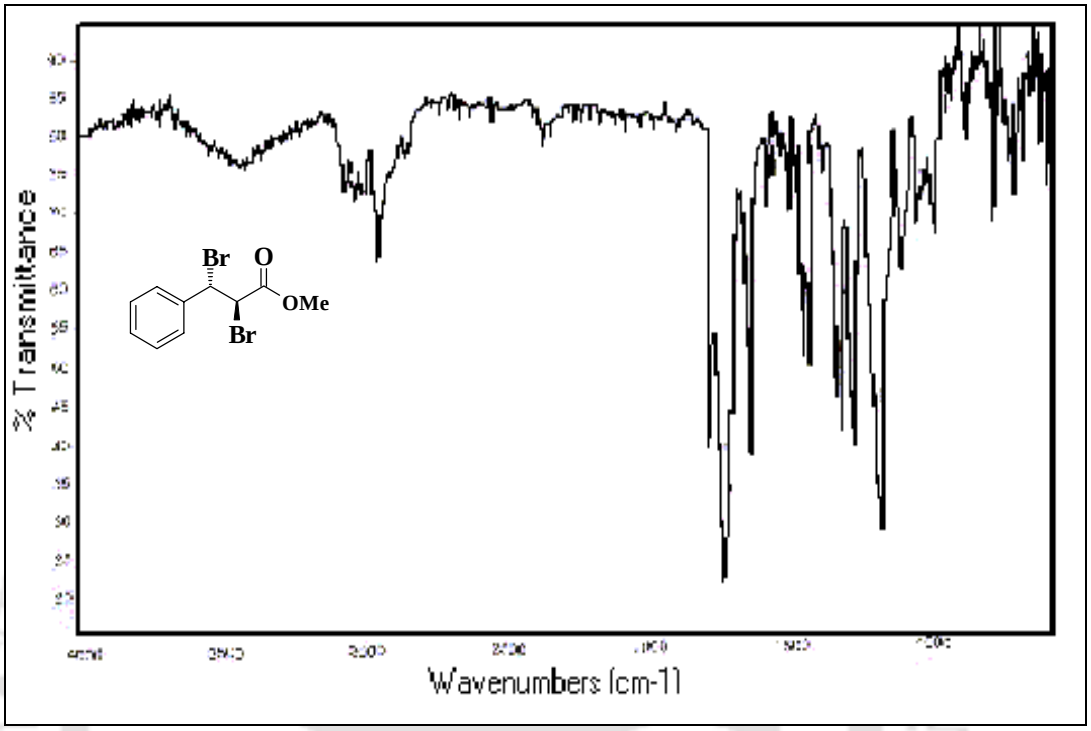


Figure 3.28. IR spectrum of **2,3-Dibromo-3-phenyl-propionic acid methy ester**

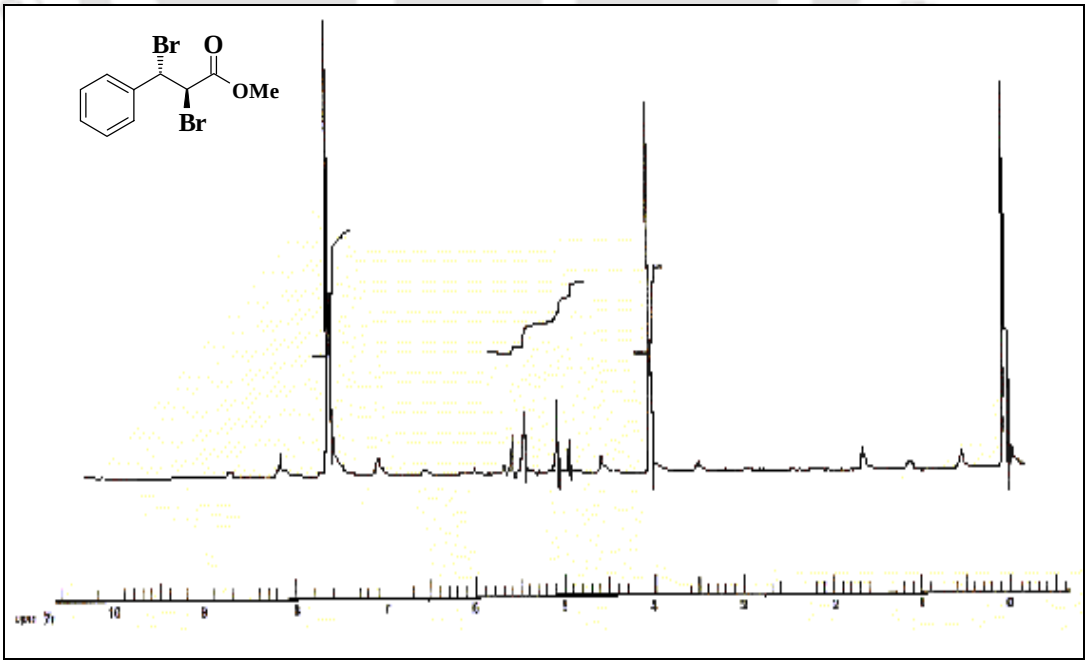
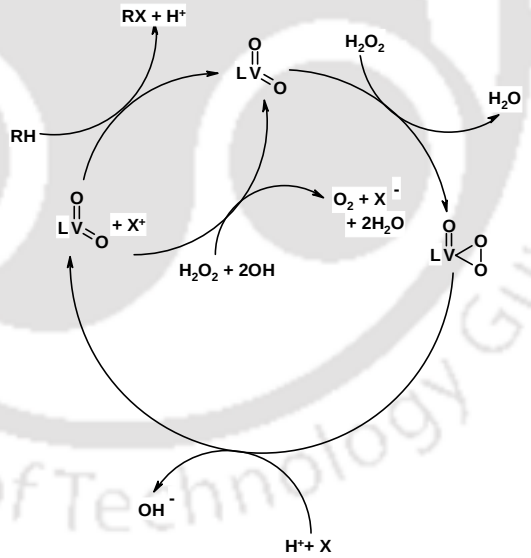


Figure 3.29. ^{1}H NMR spectrum of **2,3-Dibromo-3-phenyl-propionic acid methyl ester**

Part B

Regioselective Bromination of Organic Substrates by Tetrabutylammonium Bromide Promoted by V_2O_5-H_2O_2: An Environmentally Favorable Synthetic Protocol

In this part of Chapter 3 is presented the details of a methodology for the regioselective bromination of organic substrates by tetrabutylammonium bromide promoted by V_2O_5-H_2O_2 in an environmentally benign way. Taking cues from the knowledge of the activity of vanadium bromoperoxidase (VBrPO),[12] which catalyses bromination of marine natural products (Scheme 3.2),

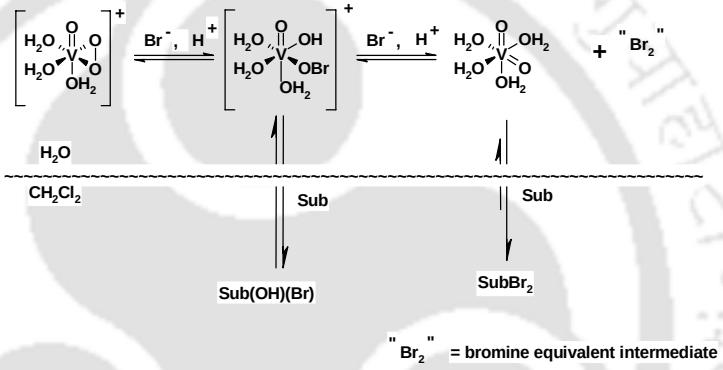


Scheme 3.2 Proposed Catalytic Cycle for the Vanadium Haloperoxidases

as well as our earlier experience of the reactivity of peroxovanadium systems,[37] we have now developed an environmentally acceptable bromination protocol involving V_2O_5 as a promoter and hydrogen peroxide and tetrabutylammonium bromide (TBAB) as the sources of active oxygen and bromide, respectively. While the

solvent of choice is a combination of acetonitrile and water, the promoter (V_2O_5) and the oxidant (H_2O_2) are both environmentally acceptable chemicals.

Literature reveals that many reactions leading to bromoorganics are conducted in bi-phasic media. And most of such reactions involve chlorinated solvents such as dichloromethane or chloroform. (Mechanism is graphically described in Scheme 3.3)[47]



Scheme 3.3. Proposed Mechanism of Vanadium Bromoperoxidases Mimicking Systems

The selection of a bi-phasic reaction medium was mainly based on the assumption that the proteic backbone of the enzyme has two different regions characterized by a largely lipophilic character (Figure 3.30)[48] suggesting thereby that a two-phase system could be a better model for VBrPO activity.

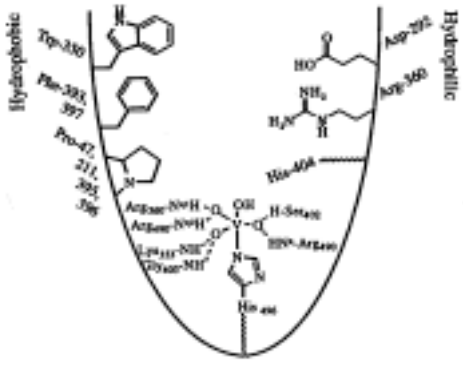


Figure 3.30. The Active Site Channel

However in the methodology of *in situ* bromination developed by us (present work), acetonitrile has been used in combination with water, and pleasantly enough the methodology worked very well yielding a wide array of bromoorganic compounds under very mild experimental conditions.

Table 3.8. Bromination of Aromatics and Some Other Substrates with TBAB and V_2O_5-H_2O_2

substrate	t/h	product	yield %
aniline	0.5	4-bromoaniline	82
acetanilide	2	4-bromoacetanilide	92
o-cresol	1.5	4-bromo- *o*-cresol	92
m-cresol	0.5	4-bromo- *m*-cresol	60
phenol	1	2,4,6-tribromophenol	98
β-naphthol	1	1-bromo-*β*-naphthol	76
anthracene	1	9,10-dibromoanthracene	93
cyclohexene	2	1,2-dibromocyclohexane	70
crotyl alcohol	2	2,3-dibromo-1-butanol	60
2-butyne-1,4-diol	1.5	2,3-dibromo-2-butene-1,4-diol	46
cyclohexanone	2	2-bromocyclohexanone	52
4-hydroxycoumarin	1	α,α-dibromo-*o*-hydroxy acetophenone	55
4-benzyloxy-4′,6′-dimethoxy -2′-hydroxychalcone	1	4-benzyloxy-3′-bromo-4′,6′- dimethoxy -2′- hydroxychalcone	72
2′-hydroxy-4,4′,6′-trimethoxy-chalcone	1	3′-bromo-4,4′,6′- trimethoxy-2′-hydroxy- chalcone	70

EXPERIMENTAL SECTION

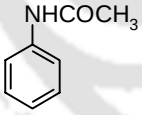
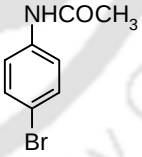
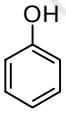
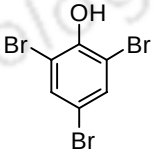
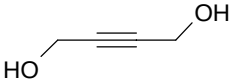
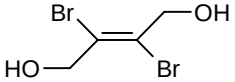
Bromination of Organic Substrates with Tetrabutylammonium Bromide (TBAB) and V_2O_5 – H_2O_2: A Typical Procedure

Bromination of Acetanilide: To an amount of 5.4 mL (48 mmol) of 30% H_2O_2 taken in a round-bottomed flask at 0 – 5 °C was added 0.27 g (1.5 mmol) of V_2O_5. The mixture was stirred for *ca.* 10 minutes, and to the solution 2.9 g (9 mmol) of

tetrabutylammonium bromide (TBAB) was added, followed by the addition of 0.4 g (3 mmol) of acetanilide. The resulting solution was stirred at *ca.* 5 °C until TLC and GC detected no starting material. To the reaction solution 30 mL ethyl acetate was added and the organic compound was extracted into the organic layer. The solvent was removed by reduced pressure distillation and the crude residue purified by column chromatography (silica gel; hexane: ethyl acetate) to afford the corresponding 4-bromoacetanilide in 92 % yield (0.63 g). The melting point of the product was 165 – 169 ºC. (lit. m.p. 167 – 169 ºC)[49]

A large variety of substrates (Table 3.8) have been brominated by this methodology. The examples given below are cited as representative examples in the present thesis. (Table 3.9)

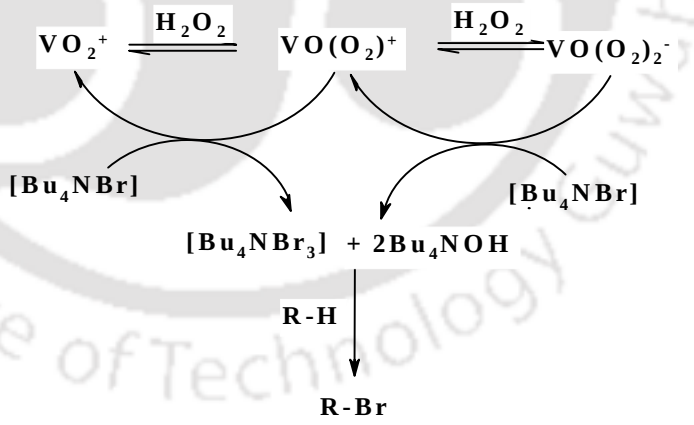
Table 3.9. Bromination of Organic Substrates by TBAB and V_2O_5-H_2O_2

substrate	t/h	product	yield (%)
	2		92
	1		98
	1.5		46

RESULTS AND DISCUSSION

STRATEGY FOR THE OXIDATIVE BROMINATION OF ORGANIC COMPOUNDS

The methodology for regioselective bromination of organic substrates is based on three main considerations. These are (i) activation of dioxygen by the interaction of H_2O_2 with vanadium(V) leading to the formation of peroxovanadium(V) species (λ = 430 nm)[37] in solution followed by (ii) oxidation of bromide by the peroxovanadium(V) intermediate ultimately leading to the formation of Br_3^- (λ = 266 nm)[16,17] as the active brominating agent, and finally (iii) bromination of organic substrates to afford bromoorganics. The wavelengths listed in parentheses were used experimentally to characterize the species present in the methodology, lending credence to the contention.



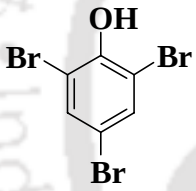
Scheme 3.4. Oxidative Bromination of Organic Substrates

In order to optimize the proportion of reactants various conditions were sampled with a result that a 1 : 3 : 0.5 : 16 substrate to tetrabutylammonium bromide to V_2O_5 to H_2O_2 stoichiometry appeared optimal (ostensibly to speed conversion to

products with high yields) and that CH_3CN/H_2O (1 : 1, 8 mL/mmol of TBAB) solvent gave very good yields. The bromination reactions were conducted at *ca.* 5 °C with stirring for the time period shown for each substrate in Table 3.8 and also Table 3.9. Scheme 3.4 is a graphical representation of the bromination reactions.

CHARACTERIZATION OF THE BROMINATED COMPOUNDS

The brominated products were characterized by IR, ^{1}H NMR (Figures 3.31 – 3.36) spectroscopic techniques, as well as by melting point measurements.

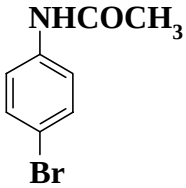


Name 2,4,6-Tribromophenol

M.p. 92 - 94 °C

IR (KBr): 3400, 2920, 2855, 1563, 1470, 1380, 1330, 1265, 1220, 1170, 964, 740, 708, 675, 555 cm^{-1}

^{1}H NMR (90 MHz, $CDCl_3$): δ 7.57 (2H, s, Ar*H*), 5.88 (1H, brs, -O*H*)

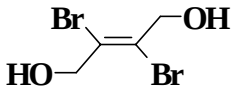


Name 4-Bromoacetanilide

M.p. 165 - 169 °C

IR (KBr): 3197, 2923, 2865, 1663, 1600, 1589, 1534, 1478, 1391, 1318, 1271, 1082, 1010, 832, 841, 748, 412 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, 2H, Ar*H*), 7.17(d, 2H, Ar*H*), 2.02 (s, 3H, -CO-CH_3)



Name 2,3-Dibromo-but-2-ene-1,4-diol

M.p. 112 - 114 °C

IR (KBr): 3255, 2920, 2865, 1445, 1440, 1375, 1370, 1240, 1080, 1020 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$+$DMSOd_6$) δ 4.41 (4H, s, 2 x -C<u>*H*</u>$_2$OH), 5.48 (2H, s. 2 x -O<u>*H*</u>)

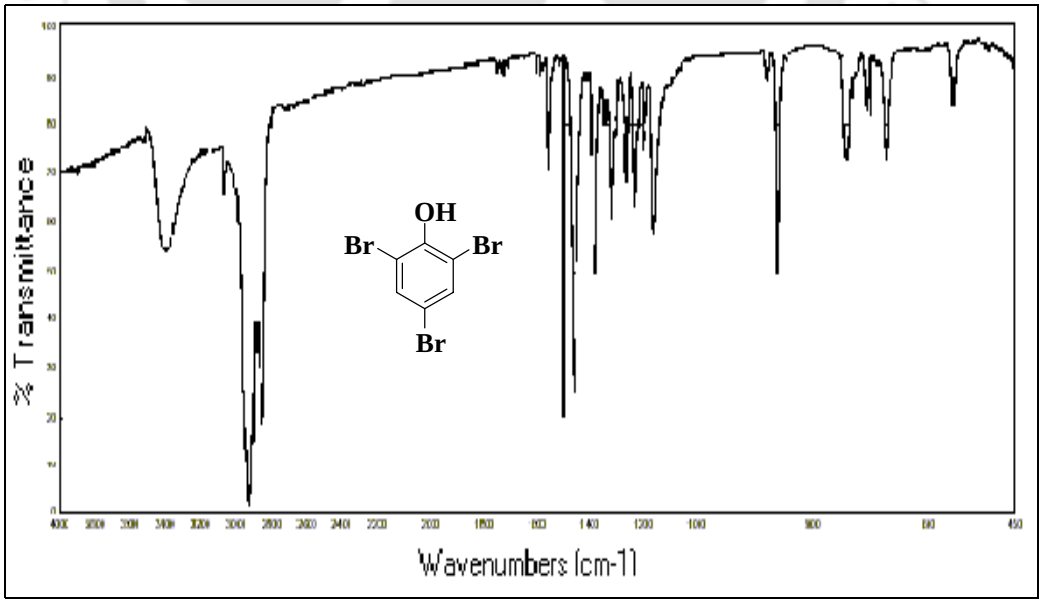


Figure 3.31. IR spectrum of **2,4,6-Tribromophenol**

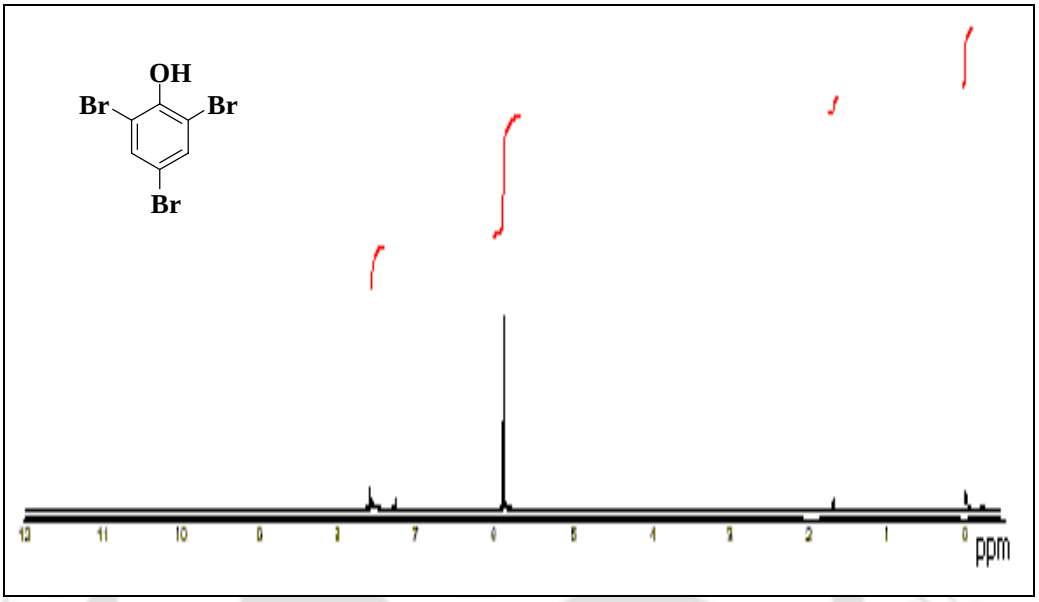


Figure 3.32. ^{1}H NMR spectrum of **2,4,6-Tribromophenol**

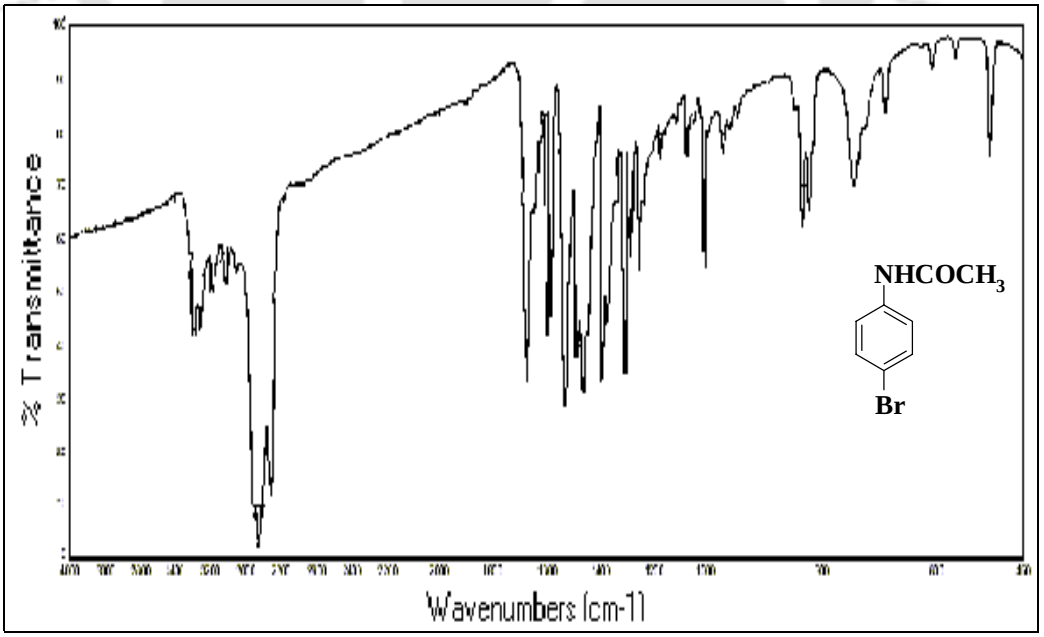


Figure 3.33. IR spectrum of **4-Bromoacetanilide**

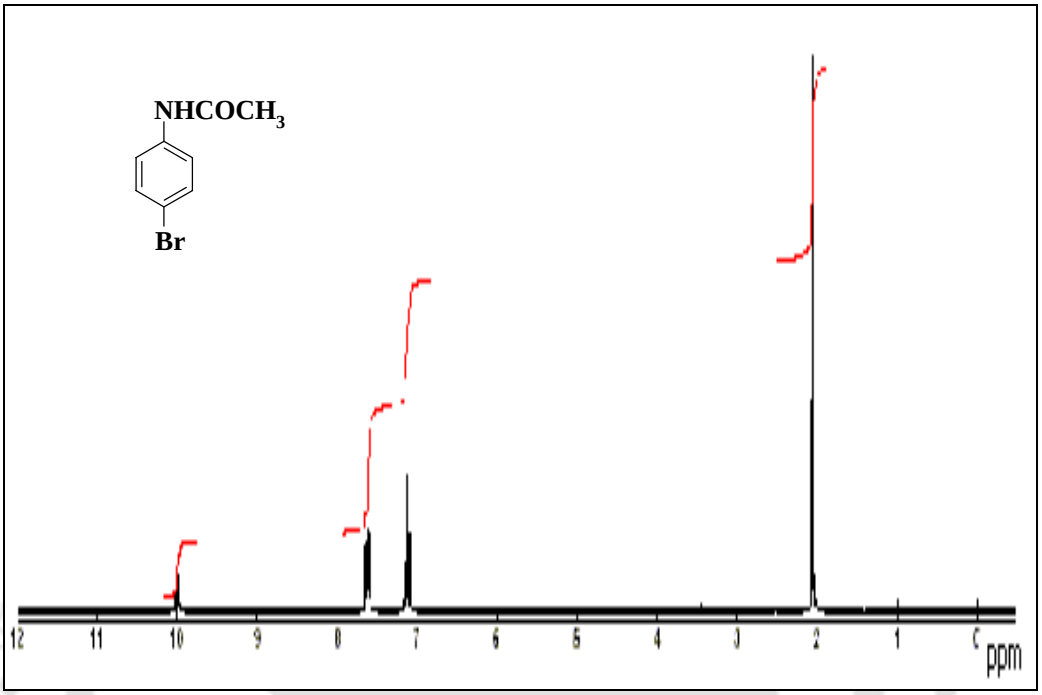


Figure 3.34. ^{1}H NMR spectrum of **4-Bromoacetanilide**

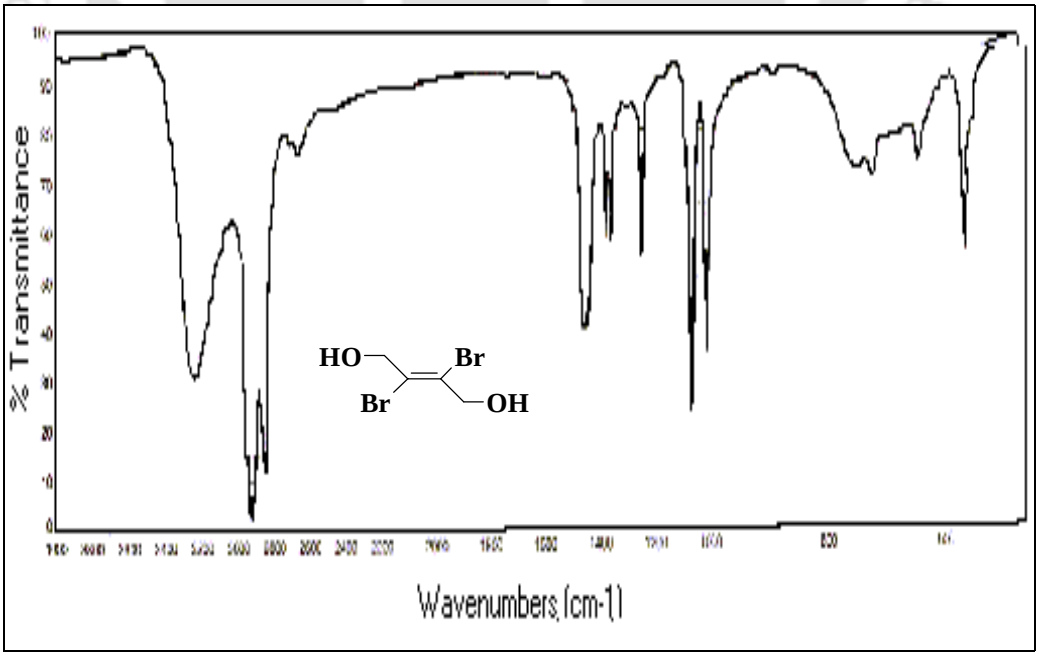


Figure 3.35. IR spectrum of **2,3-Dibromo-but-2-ene-1,4-diol**

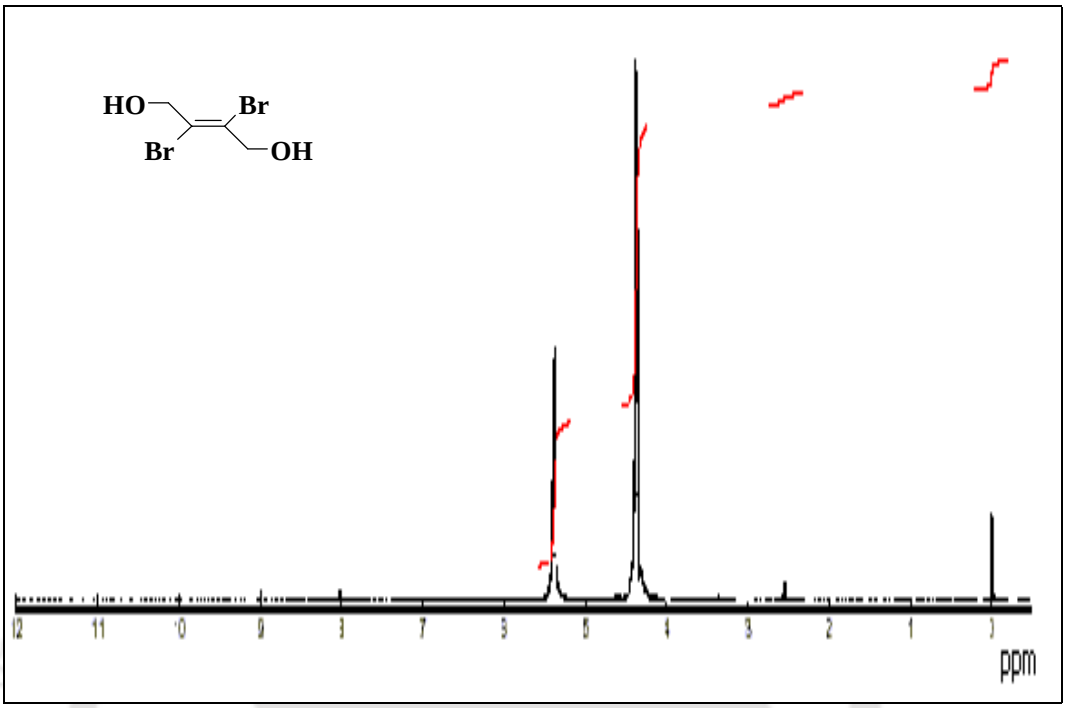
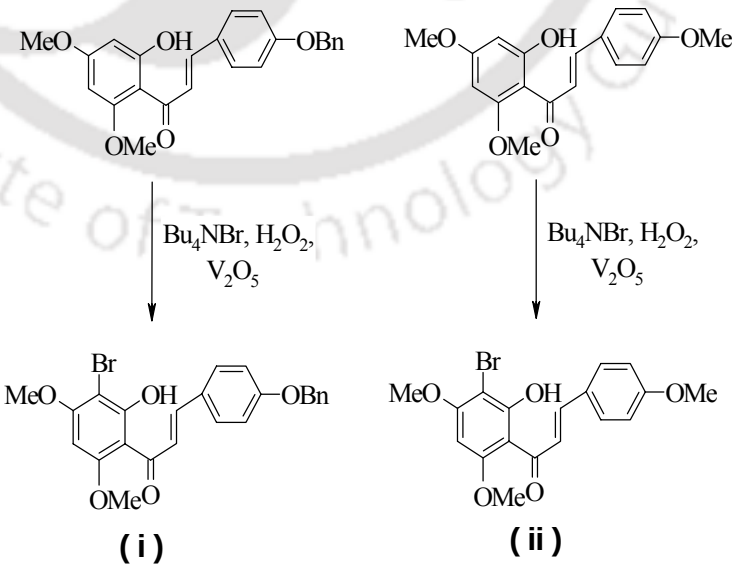


Figure 3.36. ^{1}H NMR spectrum of **2,3-Dibromo-but-2-ene-1,4-diol**

There were a few important observations made during the course of the reactions, which should be commented upon. Notably, the reaction may be conducted using a substrate: V_2O_5 molar ratio of 1 : 0.1 or 0.2; however, conversion to product is rather slow. Importantly, the intrinsic acidity of the reaction originating from dissolution of V_2O_5 in hydrogen peroxide solution not only neutralizes the hydroxide in Scheme 3.4 but also maintains the acidic reaction medium so that no extra addition of acid is required by this method (the reaction pH was *ca.* 2.1). The pH values recorded at the beginning and after completion of the reaction were *ca.* 2.0 and *ca.* 2.2 respectively. The methodology is capable of being made catalytic with KBr as the consumable source of bromide.

Quite intriguing is that the regioselective bromination of an activated aromatic compound such as acetanilide led exclusively to the corresponding *p*-bromo derivative, with similar observation being made also for aniline, *o*-cresol/and *m*-cresol (Table 3.8), while under similar experimental conditions phenol produced 2,4,6-tribromophenol. Further efficacy of the methodology lies in the bromination of alkyne systems as exemplified by the facile bromination of 2-butyne-1,4-diol. Satisfactory results were obtained also with alkenes like cyclohexene and crotyl alcohol. Notable in this context is that the molar ratio between the substrate and TBAB at 1:1, phenol and anthracene can be brominated to *p*-bromophenol (*ca.* 20 %) and 9-bromoanthracene (*ca.* 30 %) in addition to the tribromo and dibromoderivatives, respectively, if desired.

Also important is the selective bromination of the activated aromatic ring in the presence of an enone by the present methodology as shown below (Scheme 3.5):



Scheme 3.5. Some Unusual Bromination Reactions

The products 4-benzoyloxy-3′-bromo-4′,6′-dimethoxy-2′-hydroxychalcone **(i)** and 3′-bromo-4,4′,6′-trimethoxy-2′-hydroxychalcone **(ii)** are important precursors for the synthesis of the flavonoids (*c.f.,* vitexin). Very interesting is the transformation of 4-hydroxycoumarin to α,α-dibromo-*o*-hydroxyacetophenone. Indeed, α,α-dibromination of the enol form of β-ketolactone is, to the best of our knowledge, unprecedented.

Control experiments conducted by adjusting the pH to 2.1 with 0.01 M H_2SO_4, separately without involving either V_2O_5 or H_2O_2, did not bring about any change in the substrates so far examined by us.

CONCLUDING REMARKS

Peroxometal systems in general and peroxovanadium(V) in particular are versatile not only in terms of their properties, structures and uses, but also in terms of their reactivity. The newer manifestations of reaction chemistry, many of times, are capable of establishing connections between biochemically significant natural processes and laboratory-designed experimentations. The transformation of a bromide (Br^-) to a tribromide (Br_3^-) catalyzed by a peroxo-vanadium(V) intermediate in a weakly acidic medium provides a paradigmatic example for the assertion. This reaction has not only provided a general route leading to an easy access to a number of tribromides, with varying cationic size and inherent properties, that are considered as "**solid bromines**" as they are capable of delivering bromine at desired sites, but also can very safely brominates organic substrates including aromatics with high yield and selectivity. Successful preparation of quaternary

ammonium tribromides, e.g., Tetramethylammonium Tribromide (**TMATB**), $(CH_3)_4NBr_3$**,** Tetraethylammonium Tribromide (**TEATB**), $(C_2H_5)_4NBr_3$, Tetrabutylammonium Tribromide (**TBATB**), $(C_4H_9)_4NBr_3$ and Cetyltrimethylammonium Tribromide (**CTMATB**), $(C_{16}H_{33})(CH_3)_3NBr_3$ in a benign way in very high yields and the great potential they have for oxidative brominations provide an enormous scope for their use in the generation of bromoorganics, a class of commercially highly sought after compounds. A point that is highly significant and timely important is the relevance of the chemistries involved in the synthesis of the tribromides and their reactions with organic substrates (*vide* Part A of this Chapter) in the context of "**Green Chemistry**".

Interestingly, the fundamental chemistry involved in the synthesis of quaternary ammonium tribromides (**QATBs**) provided cues regarding the involvement of a peroxo-vanadium(V) intermediate leading to the generation of Br_3^- in solution. A judicial use of this knowledge has now lead to the development of very useful protocol for *in situ* generation of Br_3^- followed by its use in oxidative organic brominations of a host of different substrates, as highlighted in Part B of the present Chapter. This therefore leaves with an option for direct oxidative organic brominations without isolating the tribromides in the solid state. Philosophically, this provides a very important knowledge suggesting that a higher-valent metal that is capable of activating peroxide should be good enough to perform such transformation in the presence of a suitable bromide thereby expanding the scope of such metal-assisted oxidative brominations of organic molecules. Here again, the protocol is environmentally very clean and therefore its life is expected to be very

long. Also what is very important to note is that, if the consideration of the low cost of liquid Br_2 does not get a very high priority, the methodology developed and described herein by us should be becoming state-of-the-art for commercial exploitation. The science involved in the investigation described in Chapter 3, therefore deserves a lot of attention of the contemporary chemists. And it is hoped that this work will be the source of inspiration for a lot of new works to emerge in the years to come. Indeed there have been enough indications for what has been predicted above as evident from publications[50-54] that have been originating from several laboratories.

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SYNTHESIS AND STRUCTURAL ASSESSMENT OF DIPEROXOVANADATE(V) COMPLEXES CONTAINING 3,5-DIMETHYLPYRAZOLE AS THE HETEROLIGAND

Chapter 4

In the recent past there has been an increasing interest in heteroligand diperoxovanadates(V) which in turn has been providing impetus to establishing rational synthetic routes to such complexes. The reason for this can be the potential of these complexes to act as models for understanding biologically important molecules, besides being shown to be capable of oxidizing both inorganic and organic substrates. Literature survey reveals that diperoxovanadium(V) compounds have been implicated to be actively involved in a very important biochemical process i.e., in insulin mimicking activity.[1] The insulin mimetic behavior of vanadate(V) in solution with hydrogen peroxide has been well established, with evidences strongly suggesting that peroxovanadates are responsible for the effects observed.[2] In fact, the insulin-like synergistic effects of hydrogen peroxide with vanadate exceed those seen with vanadate or hydrogen peroxide alone.[3]

The term diabetes mellitus describes a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Insulin therapy is the only treatment for diabetic patients.[4]

The ability of diperoxovanadium(V) compounds to mimic insulin was first reported in 1987 by Posner and co-workers.[5,6] Since then there has been an immense interest in the design of water soluble diperoxovanadates, suitably ligated, that can mimic the insulin activity, and continuing work by several groups including ours[7] has resulted in the synthesis of a few such complexes. However, the successful synthesis of such compounds can be rather challenging with the synthetic reactions

being highly pH sensitive. Our involvement in this chemistry started in 1987 with the isolation of a diperoxovanadium(V) complex having ethylene diammine as the heteroligand.[7] In continuation of our endeavour in this direction we have now succeeded to gain an access to $[VO(O_2)_2dmpz]^-$, though we had earlier failed to synthesize the corresponding imidazole derivative.

However, Crans *et al.* recently reported the synthesis of a new bisperoxovanadate(V) imidazole compound having equal or greater insulinomimetic potency than that described for previously characterized peroxovanadium compounds.[1] Figure 4.1 is the structural representation of the bisperoxooxovanadate(V) imidazole monoanion.

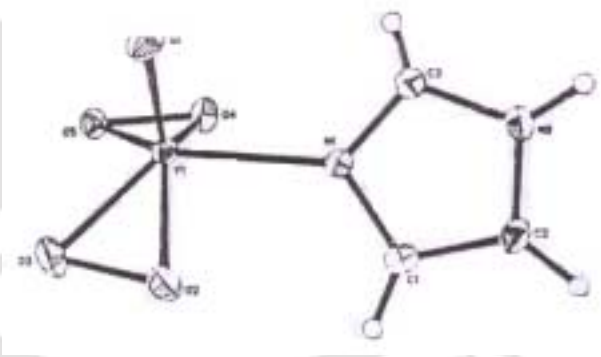


Figure 4.I. Structure[1] for the Bisperoxovanadium Imidazole Monoanion. Hydrogen atoms are omitted.

An interest in the design and development of such heteroligand peroxovanadate complexes is also because they are amenable to electronic spectroscopic studies. The study of electronic structures of the metal-dioxygen unit is of particular interest in relation to bonding of O_2 to the metal centers in metalloenzymes, oxygen-carrying proteins, and also to catalytic oxidation.[8]

In any inorganic synthesis, the choice of ligand is highly important. Taking peroxo-vanadates as a case in point, it is known that heteroligand peroxocompounds are comparatively more stable than the simple peroxo compounds.[9] 3,5-Dimethyl pyrazole is a good ligand for study as it allows some light to be shed on the nature of histidine-containing binding sites in vanadoproteins and other metallobiomolecules.[10] Although pyrazole complexes of vanadium(II) and (III) have been known for quite some time, very little work appears to have been done with vanadium(IV) or (V) except probably those reported by C. J. Carrano *et al*. The pyrazole complexes of oxovanadium(IV) and (V) have the potential to show some unusual features.[10] The doubly bound oxo groups of a dioxovanadate(V) species have an inherently irregular coordination geometry in which the weakly bound trans ligands may be readily exchanged. In this situation, the pyrazole ligands with protonated and deprotonated nitrogens as ring neighbors possess an intriguing potential for structural modifications through secondary bond interactions. Here the deprotonated nitrogen can coordinate the metal while leaving the hydrogen atom of the protonated nitrogen free to hydrogen-bond with appropriate ligands in its vicinity.

As a part of the present Ph.D research, a few heteroligand diperoxovanadate(V) complexes were synthesized having, in their coordination sphere 3,5-dimethyl pyrazole (dmpz) as the heteroligand of choice, while 3,5-dimethyl pyrazolium cation $(DmpzH)^+$, K^+, NH_4^+, and Na^+ were the cations used as counter-cations. The compounds that were thus synthesized were **DmpzH[$VO(O_2)_2$(dmpz)]**, **K[$VO(O_2)_2$(dmpz)].H_2O**, **NH_4[$VO(O_2)_2$(dmpz)].H_2O**

and **Na[VO(O$_2$)$_2$(dmpz)].2H$_2$O**. Characterization of the complexes was made on the basis of elemental analyses and a variety of spectroscopic studies. It may be mentioned that the compounds reported in this Chapter exhibit a rather typical electronic spectral pattern and may provide an excellent scope for study of the peroxo-metal interactions in solution.

EXPERIMENTAL SECTION

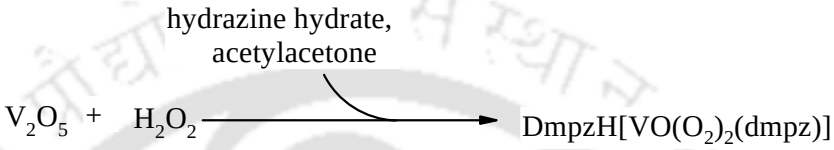
All the chemicals used were of reagent grade. The sources of the chemicals and solvents have all been already given in Chapter 2. Quantitative determination of elements was accomplished by the methods described in Chapter 2. The details of all the equipment used for physico-chemical studies are also provided in Chapter 2.

SYNTHESIS OF DIPEROXOVANADATES(V)

Synthesis of DmpzH[VO(O$_2$)$_2$(dmpz)] (1)

An amount of 0.5 g (2.76 mmol) of vanadium pentoxide, V_2O_5, was added to 10 mL (88.75 mmol) of 30 % hydrogen peroxide taken in a pre-cooled (*ca.* 0 °C) 100 mL Borosil beaker. The reaction mixture being maintained at *ca.* 0 °C was stirred till all the V_2O_5 dissolved and the solution became reddish-brown. (*Care should be taken to maintain ice-cold conditions as the reaction between V_2O_5 and H_20_2 is exothermic.*) To the clear solution 2 mL (41.2 mmol) of pre-cooled hydrazine-monohydrate, $N_2H_4.H_2O$, was added drop-wise, very slowly. (*Utmost care should be taken during the addition of hydrazine hydrate, as the reaction is highly exothermic, and can even be explosive at times.*) To the resultant solution was added 2 mL (19.4

mmol) of acetylacetone, $CH_3COCH_2COCH_3$, drop-wise, with stirring. The reaction solution was then stirred magnetically for 4 h under ice-cold conditions. The pH of the solution at this stage was recorded to be *ca.* 6.5. The solution was kept in a refrigerator and within 2 days light yellow flakes started precipitating out.

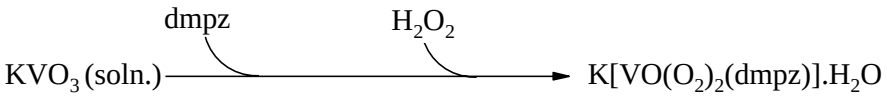


(1)

The crystals were isolated in two to three lots with the total isolation being complete in a period of seven days. The product was obtained as bright yellow flaky crystals. Yield of the product was 1.21 g (68%).

Synthesis of $K[VO(O_2)_2(dmpz)].H_2O$ (2)

An amount of 0.5 g (3.6 mmol) of potassium metavanadate, KVO_3, was added to 5 mL of water, taken in a 100 mL Borosil beaker. To the mixture an amount of 0.4 g (4.2 mmol) of 3,5-dimethyl pyrazole (dmpz) was added in small portions with stirring. The solution was then cooled in an ice-water bath till the temperature of the mixture reached 4 or 5 °C. To the cooled solution 6 mL (52.98 mmol) of 30 % hydrogen peroxide was added with stirring. The reaction solution was stirred magnetically for 3 h under ice-cold conditions. The reaction solution registered a pH value of *ca.* 6. The beaker was then placed in a refrigerator. After a period of 3 or 4 days, shiny yellow crystals started precipitating out.

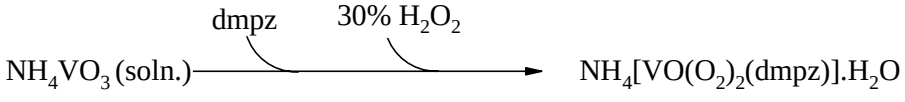


(2)

The crystals were isolated in lots and after the isolation of a crop of crystals, the mother liquor, containing a crystal as seed, was put back into the refrigerator for further precipitation of crystals. Total amount of the compound was isolated in seven or eight days from the date of isolation of the first lot of crystals. The compound was obtained as a light yellow crystalline product. The yield of the product was 0.75 g (73 %).

Synthesis of $NH_4[VO(O_2)_2(dmpz)].H_2O$ (3)

An amount of 0.5 g (4.3 mmol) of ammonium metavanadate, NH_4VO_3, was added to 5 mL of water, taken in a 100 mL Borosil beaker. To the mixture, an amount of 0.4 g (4.2 mmol) of 3,5-dimethyl pyrazole (dmpz) was added in small portions with stirring. The solution was then cooled in an ice-water bath, till the temperature of the mixture reached 4 or 5 °C. To the cooled solution, 6 mL (53.25 mmol) 30 % hydrogen peroxide was added with stirring. The reaction solution was stirred magnetically for 3 h under ice-cold conditions. The reaction mixture pH was found to be *ca.* 6 at that stage. The beaker was then placed in a refrigerator. After a period of fifteen days, shiny, deep yellow crystals started precipitating out.

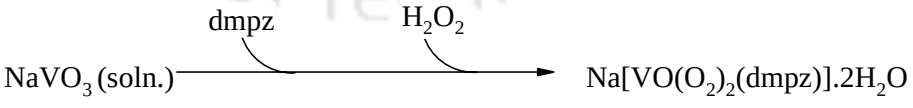


(3)

The crystals were isolated in lots and after the isolation of a crop of crystals, the mother liquor, containing a crystal as seed, was placed back in a refrigerator for further precipitation of crystals. Total amount of the compound was isolated within a week from the date of isolation of the first crop of crystals. The compound was obtained as a yellow crystalline product. Yield of the product was 0.49 g (44%).

Synthesis of $Na[VO(O_2)_2(dmpz)].2H_2O$ (4)

An amount of 0.5 g (4.1 mmol) of sodium metavanadate, $NaVO_3$, was added to 5 mL of water, taken in a 100 mL Borosil beaker. To the mixture, an amount of 0.4 g (4.2 mmol) of 3,5-dimethyl pyrazole (dmpz) was added in small portions with stirring. The solution was then cooled in an ice-water bath till the temperature of the mixture reached 4 or 5 °C. To the cooled solution, 5 mL (44.15 mmol) 30 % hydrogen peroxide was added with stirring. The reaction solution was stirred magnetically for 3 h under ice-cold conditions. The spontaneously attained pH of the reaction solution was found to be *ca.* 6.5. The beaker was then placed in a refrigerator. After a period of fourteen days, shiny yellow crystals started precipitating out.



(4)

The crystals were isolated in lots and after the isolation of a crop of crystals, the mother liquor, containing a crystal as seed, was returned to the refrigerator for further precipitation of crystals. Total amount of the compound was isolated within 9

or 10 days from the date of isolation of the first lot of crystals. The product was obtained as a yellow crystalline compound. Yield of the product was 0.59 g (51%).

ELEMENTAL ANALYSES

Quantitative estimations of vanadium, peroxide, carbon, hydrogen, nitrogen, sodium and potassium were accomplished by the methods described in Chapter 2. The analytical data of the compounds are summarized in Table 4.1. The results of the peroxide estimations by redox titration involving standard potassium permanganate suggested the presence of two peroxides per vanadium (V) center.

RESULTS AND DISCUSSIONS

SYNTHESIS

The importance of pH in the reactions of vanadium(V) with hydrogen peroxide is well acknowledged. In fact one of the essential parameters for achieving success in the synthesis of the diperoxovanadate(V) complexes was the working out of the right pH. The pH value of 6 or 6.5 was found to be conducive to the successful synthesis of the targeted complexes. A near neutral pH attained spontaneously during the reaction allowed isolation of the diperoxovanadates(V) in the solid state. It is now almost a textbook story that the heteroligand plays a very important role in stabilization of such type of complexes, thus allowing them to be isolated. The heteroligand selection is yet another art in the synthesis of such compounds. Whereas there has to be a definite relevance for a particular heteroligand to be chosen, the selected heteroligand should also be able to chemically interact well enabling a successful synthesis. Incidentally, the lone pair of the non-protonated nitrogen of

dmpz provides a good handle for establishing coordination with a higher valent metal, e.g., vanadium(V) in the present case. In the present context 3,5-dimethyl pyrazole (dmpz) does well, behaving as a monodentate ligand coordinating through the pyrazole N of the azole ring. It is believed that the heteroligand 3,5-dimethyl pyrazole being a weak base neutralizes the weak acidity arising from the H_2O_2 solution in a good part thereby rendering the reaction medium nearly neutral, as observed in the present case. It is notable in the context of the synthesis of **dmpzH[VO(O$_2$)$_2$(dmpz)]** that a somewhat different strategy had to be adopted in this case for a pre-synthesized did not provide the desired compounds, at least under present experimental conditions. The strategy then applied was that the chosen heteroligand be synthesized on the metal site itself. Accordingly, hydrazine was first allowed to coordinate with the peroxovanadate(V) formed *in situ* and thereafter acetylacetone ($C_5H_8O_2$) was allowed to react with the peroxovanadate(V) the coordinated N_2H_4 to afford the compound as obtained. The reaction might have proceeded in a manner similar to that observed for a cobalt complex[11] some years ago. An excess of dmpz available in a slightly acidic reaction solution afforded the counter cation, dmpzH. It should also be mentioned that the **dmpzH[VO(O$_2$)$_2$(dmpz)]** was much sought after by us as a companion of Crans' **imH[VO(O$_2$)$_2$(im)]** (im = imidazole),[1] a compound with a very high insulin mimicking property. The similarity of the two compounds is a clear indication of their similar properties.

CHARACTERIZATION AND STRUCTURAL EVALUATION

The diperoxovanadates(V) are all yellow, micro-crystalline compounds that are soluble in water permitting solution electrical conductance measurements. The compounds are highly soluble in water but barring **dmpzH[VO(O$_2$)$_2$(dmpz)]**, are sparingly soluble in most of the common organic solvents. The stability of the compounds is temperature dependant, and thus while **dmpzH[VO(O$_2$)$_2$(dmpz)]**, **NH$_4$[VO(O$_2$)$_2$(dmpz)].H$_2$O** and **Na[VO(O$_2$)$_2$(dmpz)].2H$_2$O** are stable at 4 °C for periods beyond three months, **K[VO(O$_2$)$_2$(dmpz)].H$_2$O** is stable at room temperature for more than six months. One of the most dependable ways of monitoring the stability is by the estimation of active oxygen content periodically. The compounds all analyzed very well.

Table 4.1. Analytical Data

compound	found % (calcd. %)				
	V	O[a]	C	H	N
DmpzH[VO(O$_2$)$_2$(dmpz)] **(1)**	15.68 (15.71)	19.24 (19.74)	36.81 (37.05)	5.18 (5.28)	17.29 (17.28)
K[VO(O$_2$)$_2$(dmpz)].H$_2$O **(2)**	17.71 (17.93)	22.21 (22.52)	21.00 (21.13)	3.08 (3.55)	9.59 (9.86)
NH$_4$[VO(O$_2$)$_2$(dmpz)].H$_2$O **(3)**	19.49 (19.36)	24.27 (24.32)	22.83 (22.82)	5.52 (5.74)	15.13 (15.96)
Na[VO(O$_2$)$_2$(dmpz)].2H$_2$O **(4)**	17.74 (17.81)	22.33 (22.37)	20.59 (20.98)	3.97 (4.24)	9.57 (9.79)

[a] Active Oxygen

The peroxide contents were estimated by redox titrations involving potassium permanganate in an acidic medium. Boric acid was used to prevent any loss of active

oxygen. Yet another important point to be noted is that the observed stoichiometry between V(V) and O_2^{2-} of 1 : 2, as evidenced by the chemical analyses. A consistent occurrence V(V) : O_2^{2-} as 1 : 2 supports the contention that the complexes are all diperoxo species. (Table 4.1)

Solution Electrical Conductance Measurements

The molar conductances (10^{-3} M, aq. soln) of the newly synthesized compounds were found to lie in the range 110-130 $\Omega^{-1}cm^2mol^{-1}$ suggesting a 1:1 electrolytic nature of each of them, which was in agreement with their formulae. The results of conductance measurements have been set out in Table 4.2.

Table 4. 2. Solution Electrical Conductance Values

compound	solution electrical conductance (10^{-3} M) ($\Omega^{-1}cm^2mol^{-1}$)
$DmpzH[VO(O_2)_2(dmpz)]$ **(1)**	122
$K[VO(O_2)_2(dmpz)].H_2O$ **(2)**	119
$NH_4[VO(O_2)_2(dmpz)].H_2O$ **(3)**	109
$Na[VO(O_2)_2(dmpz)].2H_2O$ **(4)**	125

The result of conductance experiments is not considered to be too trivial because it conveys a lot of information about the stability and retention of identity in solution, at least under the experimental conditions.

Electronic Spectroscopic Studies

In a typical case of a metal complex containing peroxides as terminal ligands, two peroxo (LMCT) bands are expected in the UV-visible region due to two types of transitions viz. $\pi_v \rightarrow d_\sigma^*$ and $\pi_h \rightarrow d_\sigma^*$.[12,13] It may be mentioned that the latter transition, which involves much higher energy, has rarely been identified[14] in the spectra of most of the peroxo complexes. However, it has been possible for us to detect this transition under carefully conducted experimental conditions. (Figures 4.2 – 4.5, Table 4.3)

Table 4.3. Electronic Spectral Data

compound		uv-vis λ (nm) (ε, $M^{-1}cm^{-1}$)
DmpzH[$VO(O_2)_2$(dmpz)]	**(1)**	330 (691) 212 (40,700)
K[$VO(O_2)_2$(dmpz)].H_2O	**(2)**	330 (700) 210.5 (49,800)
NH_4[$VO(O_2)_2$(dmpz)].H_2O	**(3)**	330 (610) 212 (16,200)
Na[$VO(O_2)_2$(dmpz)].$2H_2O$	**(4)**	329 (472) 211 (38,300)

Thus, the peroxo (LMCT) bands of the complexes **1**, **2**, **3** and **4** have been clearly resolved in aqueous solutions at ~330 and ~211 nm, respectively. The charge transfer band at ~330 nm of weak intensity has been assigned to $\pi_v \rightarrow d_\sigma^*$ transition. The band at ~211 nm is especially significant because this particular transition is not

generally observed in most cases of peroxo-metallates.[8] This absorption is assigned to the $\pi_h \rightarrow d_\sigma^*$ transition.

These results cause us to state that the complex **$[VO(O_2)_2(dmpz)]^-$** species may serve as a suitable probe for electronic absorption spectroscopic studies related to the interaction of vanadium(V) with peroxide (O_2^-) in the presence of an N-donor ligand (*cf.* imidazole). Incidentally, the spectral pattern including the band positions is similar to what has been observed for the corresponding imidazole (imz) containing complex, **$[VO(O_2)_2(imz)]^-$** .

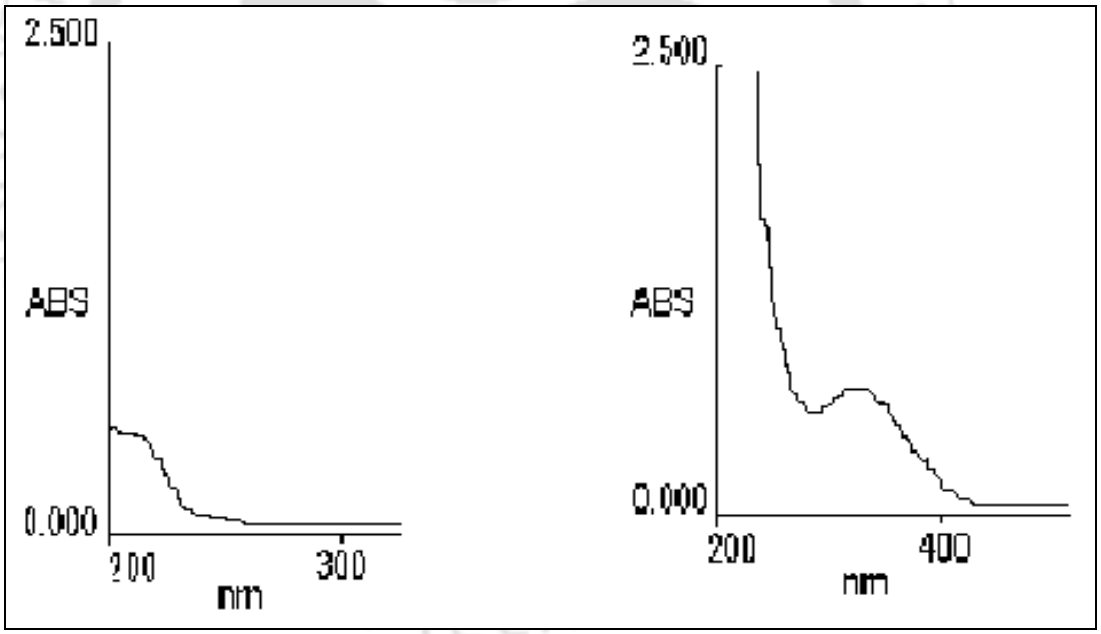


Figure 4.2 UV-absorption spectra of **DmpzH[$VO(O_2)_2(dmpz)$]** (**1**)

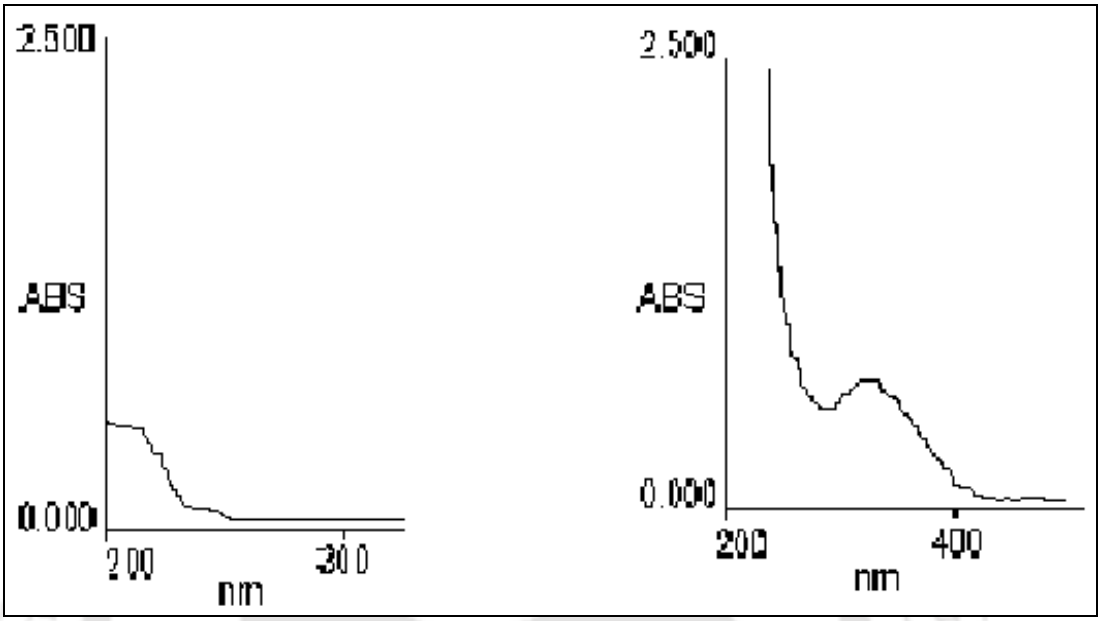


Figure 4.3 Electronic spectra of **$K[VO(O_2)_2(dmpz)].H_2O$ (2)**

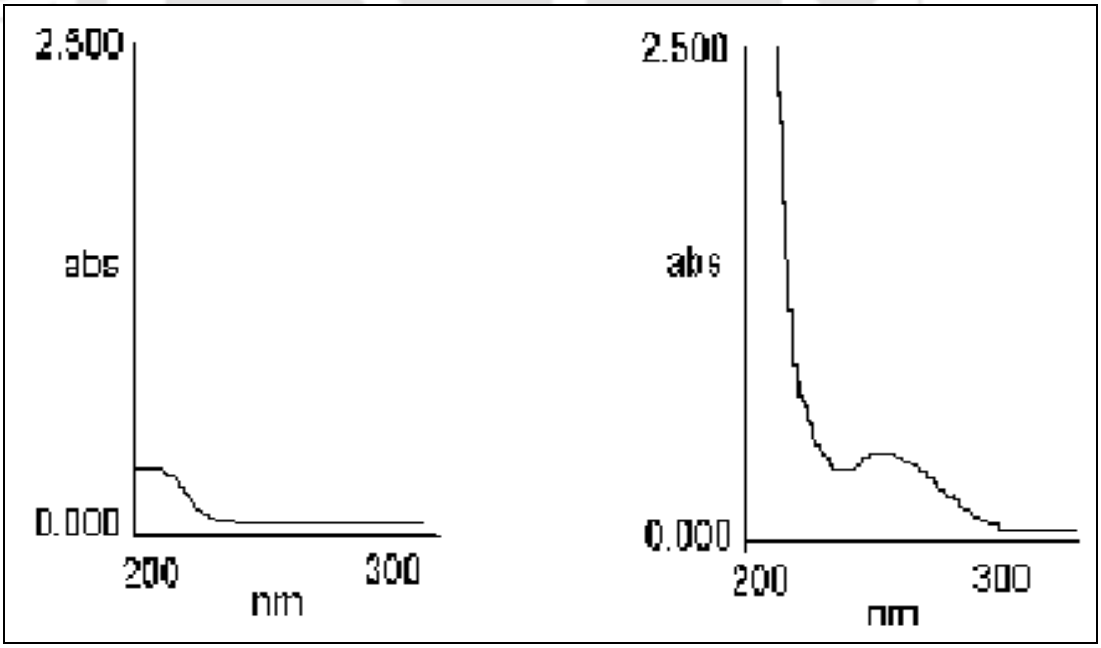


Figure 4.4 Electronic spectra of **$NH_4[VO(O_2)_2(dmpz)].H_2O$ (3)**

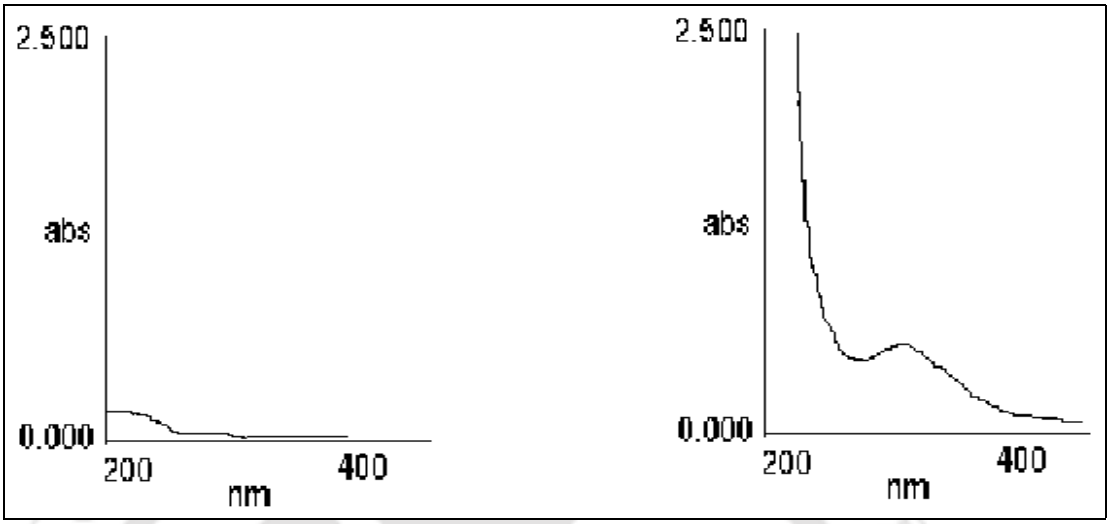


Figure 4.5 UV-absorption spectra of **$Na[VO(O_2)_2(dmpz)].2H_2O$ (4)**

Infrared Spectroscopic Studies

Vibrational spectroscopy is an essential technique for the characterization of complexes containing coordinated peroxo groups. The great majority of transition metal peroxide complexes involve a coordinated bidentate peroxide group. Bidentate peroxide coordination creates a local C_{2v} environment which has three IR active modes: the symmetric O-O stretch, the symmetric metal-peroxo stretch, and the asymmetric metal-peroxo stretch.[15-18] These vibrations occur at *ca.* 880, 600 and 500cm^{-1} respectively, although the metal-peroxo stretches are not always clearly distinguishable. The O-O stretching band is the most intense one, and characteristically occurs between 800 and 900cm^{-1}. Important it is that the frequency of this band remains fairly independent of the heteroligand environment, but is affected, at times, by the mass of the metal ion indicating coupling of the O-O stretching with M-O_2 vibrations.

Table 4.4. Structurally Significant IR Spectral Data

compound		ν (cm^{-1})	assignment
DmpzH[$VO(O_2)_2$(dmpz)]	**(1)**	942(s)	$\nu_{V=O}$
		874(s)	ν_{O-O} (ν_1)
		533(s)	ν_{V-O_2}(ν_2)
		635(s)	ν_{V-O_2} (ν_3)
		1566(s)	ν_{C-N}
		3244(b)	ν_{N-H} (dmpz)
		330(m)	ν_{V-N}
$K[VO(O_2)_2(dmpz)].H_2O$	**(2)**	943(s)	$\nu_{V=O}$
		877(s)	ν_{O-O} (ν_1)
		540(s)	ν_{V-O_2}(ν_2)
		633(s)	ν_{V-O_2} (ν_3)
		1567(s)	ν_{C-N}
		3244(s)	ν_{N-H} (coord.
		332(m)	ν_{V-N} dmpz)
		1655(m)	δ_{H-O-H}
		3410(m,b)	ν_{O-H}
$NH_4[VO(O_2)_2(dmpz)].H_2O$	**(3)**	942(s)	$\nu_{V=O}$
		876(s)	ν_{O-O} (ν_1)
		535(s)	ν_{V-O_2}(ν_2)
		624(s)	ν_{V-O_2} (ν_3)
		1567(s)	ν_{C-N}
		3250(s)	ν_{N-H} (coord.
		332(m)	ν_{V-N} dmpz)
		1653(m)	δ_{H-O-H}
		3410(m,b)	ν_{O-H}
$Na[VO(O_2)_2(dmpz)].2H_2O$	**(4)**	950(s)	$\nu_{V=O}$
		883(s)	ν_{O-O} (ν_1)
		534(s)	ν_{V-O_2}(ν_2)
		632(s)	ν_{V-O_2} (ν_3)
		1570(s)	ν_{C-N}
		3191(s)	ν_{N-H} (coord.
		332(m)	ν_{V-N} dmpz)
		1653(m)	δ_{H-O-H}
		3410(m,b)	ν_{O-H}

The infrared spectra of the series of four salts resemble each other very closely (Figures 4.6 – 4.9, Table 4.4.), indicating that the compounds are similar structurally. The IR spectra show bands at ~950, ~877, ~630 and ~530 cm^{-1} which have been assigned to $\nu_{V=O}$, ν_{O-O} (ν_1), ν_{V-O_2} (ν_3) and ν_{V-O_2} (ν_2) modes respectively. The observed positions of ν_{O-O} and ν_{V-O_2} modes, and the number of such vibrations correspond to those which one would expect to observe for triangularly bonded peroxide ligand, and accordingly it is argued that the peroxide ligands are bonded to the vanadium (V) center in a triangular bidentate (C_{2v}) manner in each of the newly synthesized compounds. The ν_1 mode is well separated from the ν_2 and ν_3 modes and the band at ~877 cm^{-1} is unambiguously assigned to the ν_1 (ν_{O-O}) mode of coordinated peroxide (O_2^{2-}).

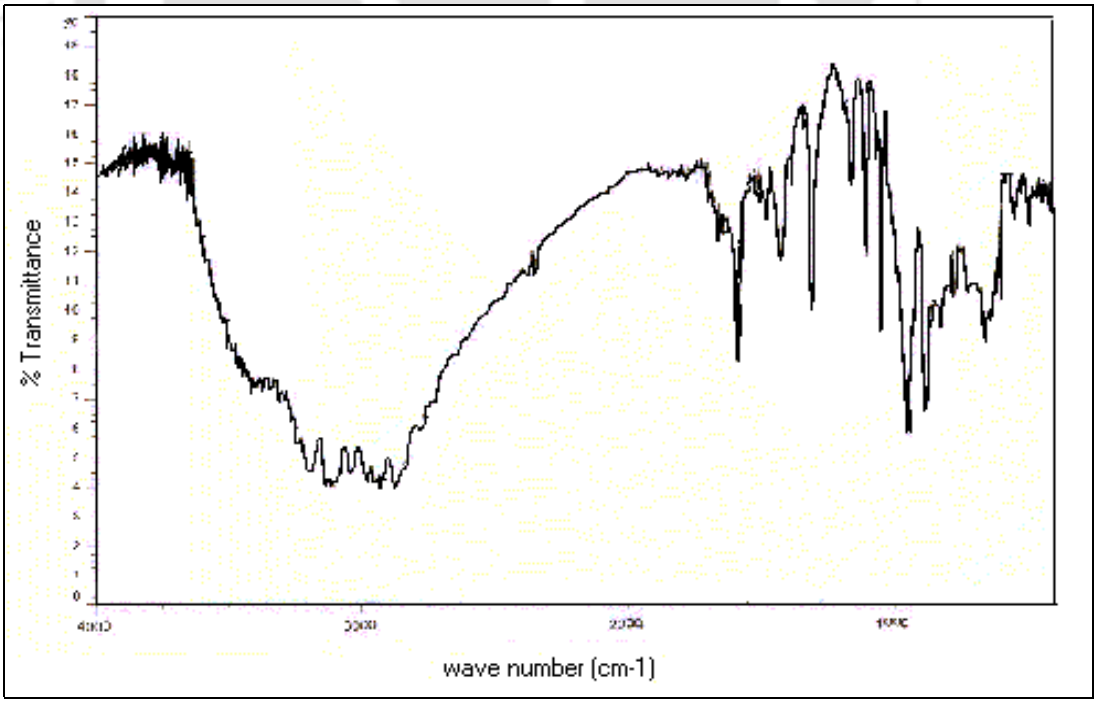


Figure 4.6 IR Spectrum of **DmpzH[VO(O$_2$)$_2$(dmpz)]** (**1**)

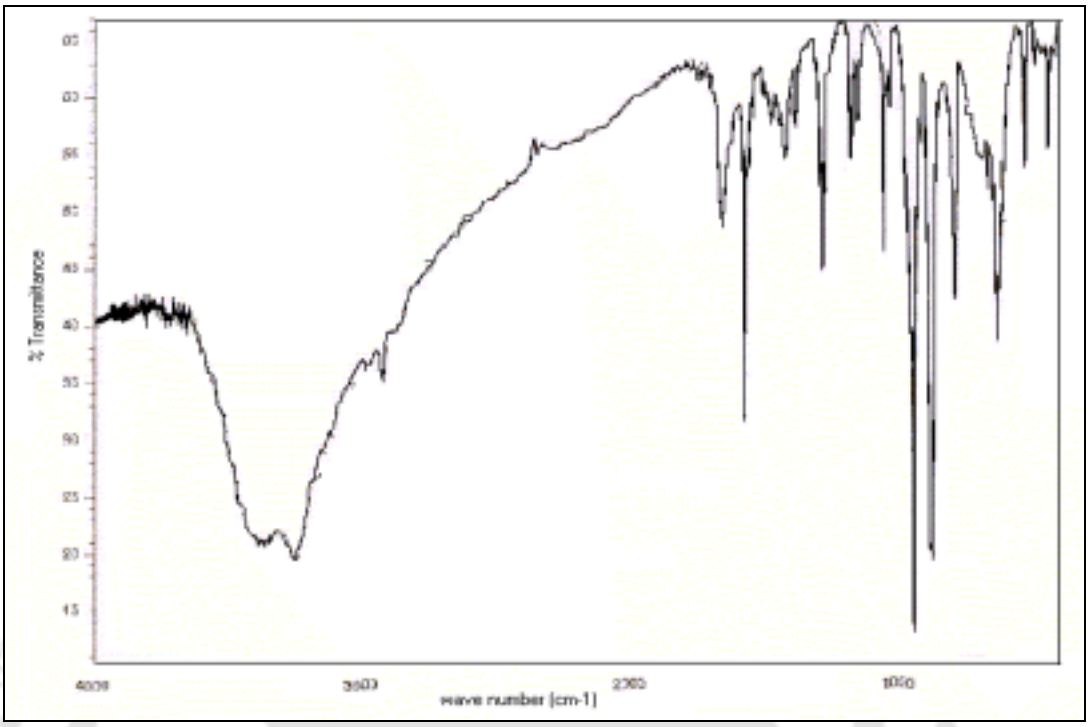


Figure 4.7 IR Spectrum of **$K[VO(O_2)_2(dmpz)].H_2O$** (**2**)

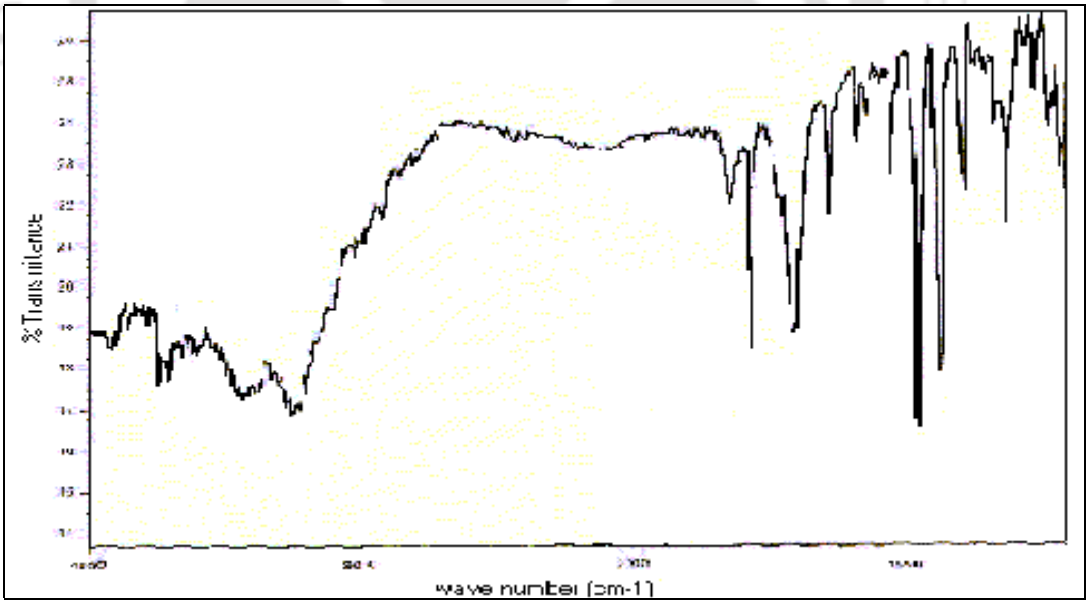


Figure 4.8 IR Spectrum of **$NH_4[VO(O_2)_2(dmpz)].2H_2O$ (3)**

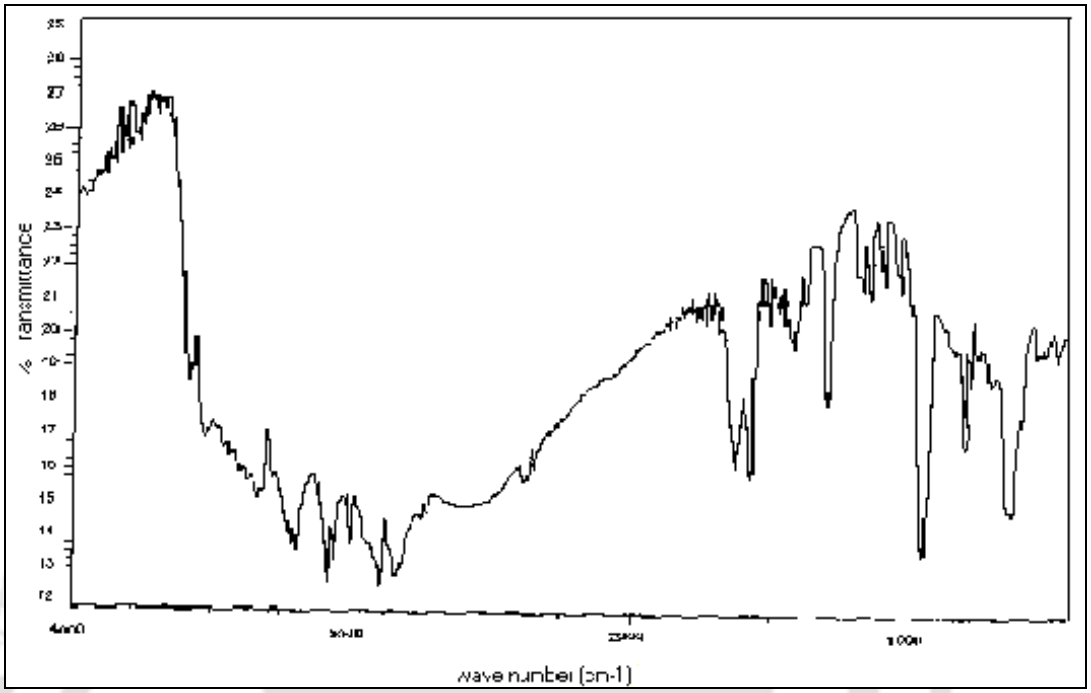


Figure 4.9 IR Spectrum of **$Na[VO(O_2)_2(dmpz)].2H_2O$** (**4**)

The strong absorption at ~950cm^{-1} owes its origin to the presence of a terminally bonded oxygen atom.

The spectral pattern originating from the presence of dmpz ligand is quite representative of its monodentate coordination to the metal center.[19-21] Importantly, a positive shift of the $\nu_{C\text{-}N}$ (pyrazole ring) band by about 12 cm^{-1} compared to that of the free ligand suggests that the tertiary ring nitrogen possibly provides the binding site. This contention gains further support from the appearance of a band at *ca.* 3240 cm^{-1} owing its origin to $\nu_{N\text{-}H}$. In other words, it is the non-protonated nitrogen that appears to be bonded to the V(V) center. It is quite likely that the electrons on the protonated nitrogen form a part of the aromatic sextet thereby rendering it unavailable for coordination. The observance of $\nu_{C\text{-}N}$ at *ca.* 330 cm^{-1} (not shown in

Figures 4.6 – 4.9) provides additional support to the monodentate coordination of the dmpz ligand in the present cases.

Another notable feature of the IR spectra of complexes **2**, **3** and **4** (Figures 4.7 – 4.9), were two additional bands observed at ~1653 and ~3410 cm^{-1}, which resemble in their shapes and positions to those commonly observed for uncoordinated water[22] and have been accordingly assigned to the $\delta_{H\text{-}O\text{-}H}$ and $\nu_{O\text{-}H}$ modes, respectively.

^{1}H NMR Spectroscopic Studies

The ^{1}H NMR spectrum of **dmpzH[VO(O$_2$)$_2$(dmpz)]** against TMS evidences for the occurrence of both coordinated dimethylpyrazole ligand and 3,5-dimethylpyrazolium cations (300 MHz, $CDCl_3$) δ 2.27 (s, 12 –C<u>H</u>$_3$), 5.55 (bs, 3H, -N<u>H</u>), 5.85 (s, 1H, =C<u>H</u>-) ppm. This gets along with the formula of the compound **1**.

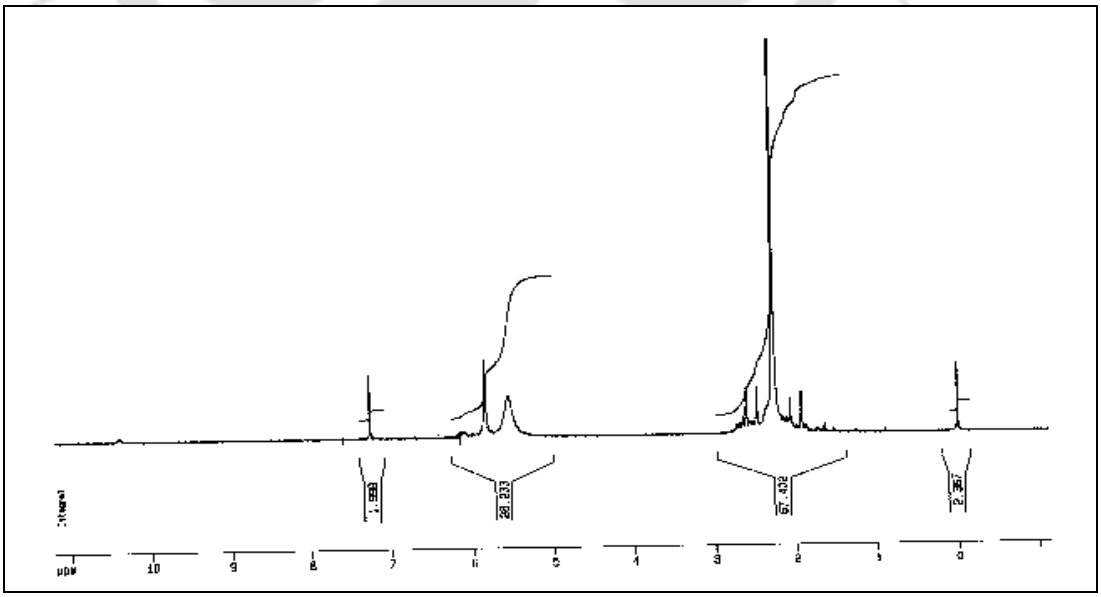


Figure 4.10 ^{1}H NMR spectrum of **DmpzH[VO(O$_2$)$_2$(dmpz)] (1)**

X-ray Crystallography

Ideally, the structural delineation by X-ray crystallographic studies would be preferred to confirm the structure of the complex, **$[VO(O_2)_2(dmpz)]^-$**, ion. Unfortunately, non-availability of such a facility at our work place in conjugation with instability of the compounds precluded such an investigation to be conducted, so far. However, a strong similarity between the vibrational spectral bands of **$[VO(O_2)_2(dmpz)]^-$** and **$[VO_2F(dmpz)_2]$**, in **so far as the vanadium — dmpz binding is concerned**, occurrence of vanadium(V) in both the cases, and availability of the X-ray crystallographically generated structural data pertaining to the presence of V — N (dmpz) of the dmpz ligand being bonded to the metal center in a monodentate fashion (mean V - N distance is 2.11 Å) renders us to believe that the 3,5-dimethylpyrazole (dmpz) ligand in **$[VO(O_2)_2(dmpz)]^-$** is coordinated to vanadium(V) in a manner similar to that of the complex **$[VO_2F(dmpz)_2]$**, as shown in Figure 4.11.

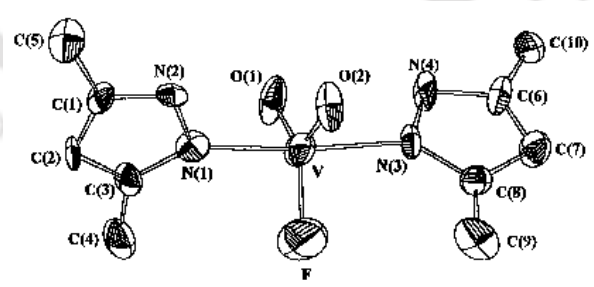


Figure 4.11 ORTEP Drawing of $[VO_2F(dmpz)_2]$ Showing the Thermal Ellipsoids and Atomic Numbering Scheme. Hydrogen atoms are omitted for clarity

TG experiments showed that compounds **2**, **3** and **4** lose water at 105-120 ºC, suggesting thereby that the water molecules are not coordinated (lattice water) to the metal. Relevant in this context is to note that the compound

dmpzH[VO(O$_2$)$_2$(dmpz)] (**1**) does not contain any water. Considering all these, it may be quite safe to state that the V(V) centre in the complex **[VO(O$_2$)$_2$(dmpz)]$^-$** is hexa coordinated with a structure presumably similar to that of **[VO(O$_2$)$_2$(imz)]$^-$** (i.e. nearly a pentagonal pyramid), as ascertained by Crans *et al*.[1] This could be one of the rare examples of hexacoordinated peroxovanadium(V) complexes. The two very well established examples of this type include **[VO(O$_2$)$_2$(NH$_3$)]$^-$** [23] and **[VO(O$_2$)$_2$(imz)]$^-$** .[1] It may be significant to note that the N-donor ligand in each is or acted as a monodentate ligand. Whether this sort of ligation has any thing to do with the hexacoordination of V(V) is a matter which needs to be addressed.

CONCLUDING REMARKS

The compounds of the type **A[VO(O$_2$)$_2$(dmpz)].xH$_2$O** [A = NH_4 or K, x = 1, A = Na, x = 2] and **dmpzH[VO(O$_2$)$_2$(dmpz)]** have now been synthesized, although we failed earlier to prepare the analogous imidazole ligated complexes. The synthesis is in general somewhat tricky in a sense that while compounds **2**, **3**, and **4** can be obtained from the reactions of the corresponding AVO_3 directly with the heteroligand, 3,5-dimethylpyrazole (dmpz), and 30 % H_2O_2 at pH 6-6.5, compound **1**, **dmpzH[VO(O$_2$)$_2$(dmpz)]** could not be obtained by the same protocol. What was required for **1** was to synthesize the heteroligand on the metal. The strategy was that the reaction of V_2O_5 with 30 % H_2O_2 would generate peroxovanadate(V) species in solution that would first interact with hydrazine in solution. The mixed ligand peroxovanadate(V) complex containing hydrazine as the heteroligand would then be allowed to react with acetylacetone ($C_5H_8O_2$) so as to enable formation of 3,5-

dimethylpyrazole (dmpz) through a condensation reaction between hydrazine and dmpz. A similar synthesis was done by us on cobalt(II) centre several years ago.[11] The reaction strategy worked very well finally affording the compound that we have long been looking for. The compound **dmpzH[VO(O$_2$)$_2$(dmpz)]** is a direct companion of Crans' **imzH[VO(O$_2$)$_2$(imz)]**[1] in terms of the similarity in composition, coordination number of V(V) in the complex and solubility in aqueous medium thereby satisfying the properties which we desired such a compound to possess. One of the important concerns has been to generate suitable peroxovanadate(V) complexes with enhanced insulinomimetic properties. To this end results of such investigations involving **1** are awaited before any comment on its potential as an insulinomimic is made.

Also significant is the less usual six-coordination geometry of the metal centre in a heteroligand peroxo-environment. Our endeavour is on to grow good X-ray quality crystals so as to enable us ascertain the structure of **[VO(O$_2$)$_2$(dmpz)]$^-$** in collaboration with another group of workers having X-ray facilities. However, the direct parallism between the spectroscopically delineated binding modes of dmpz with V(V) in **[VO$_2$F(dmpz)]**[24] which has been also X-ray crystallographically characterized, and **[VO(O$_2$)$_2$(dmpz)]$^-$** (present work), in conjugation with our experience in dealing with different types of peroxovanadates(V) provide clear and quite convincing indication for the occurrence of a monodentate dmpz ligand in the presently synthesized heteroligand peroxovanadate(V) complexes. Compounds **1** – **4** also leave us with a great scope of further studies on their biological and chemical reactivity profiles.

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*OXIDATION OF SELECTED ORGANIC SUBSTRATES USING A NEW REAGENT, 3,5-DIMETHYLPYRAZOLIUM FLUOROCHROMATE(VI), $C_5H_8N_2H[CrO_3F]$, DmpzHFC**

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The work described in this Chapter has been pulished:

(i) *Tetrahedron*, **2001**, *57*, 2445.

Chapter 5

Partial oxidations of organic substrates have always been commercially very important and for this purpose no other reagent could be as popular, as useful and as successful as the chromium(VI) reagents have been, with the ones next in order of efficacy being those based on MnO_4^- [*c.f.* Mn(VII)].[1] Though there are some limitations of chromium reagents in terms of environmental antagonism, the popularity of such reagents does not seem to diminish because of their performance under mild conditions with high efficiency and cost-effectiveness weigh far over their limitations. Thus, chromium(VI) based oxidizing agents have been extensively worked on leading to the development of a good number of reagents, many of which have become quite popular and performing well as oxidizing agents. Some of the important entries in the list of chromium(VI) reagents are the Collin's reagent,[2] chromium-trioxide-3,5-dimethyl-pyrazole complex,[3] pyridinium chlorochromate (**PCC**),[4,5] pyridinium dichromate (**PDC**)[6] and 2,2′-bipyridinium chlorochromate (**BiPCC**).[7] In addition, there are a few other systems which work as reagents in combination with chromium(VI), e.g., chromium(VI)—*t*-butylhydroperoxide,[8-11] chromium(VI)— peroxocarbonate[12,13] and chromium(VI) — peroxoborate.[14]

Over several years our group has been involved in developing newer reagents and methodologies allowing oxidations to be performed under mild conditions.[15-20] Our participation in the development of newer chromium reagents led to the introduction of reagents like pyridinium fluorochromate (**PFC**)[15] and quinolinium fluorochromate (**QFC**)[18] as oxidants with improved properties in terms of higher solubility and controlled acidity. An ever-increasing use of **PFC** as a versatile

oxidant attests to its credibility as a popular reagent. This reagent has not only survived the test of time but also been continuously showing newer applications with the passage of time.[21-25] It is highly encouraging to see the width of the spectrum of the reagent. However, as it often happens with even the best of the reagents, that it does not fare well with some specific cases and pyridinium fluorochromate (**PFC**) is no exception in this respect. And this could only be ascertained when the reagent was applied to steroidal oxidations. Specifically we have been interested in the oxidation of Δ^5- steroids because Δ^5- steroids with keto functionality at the 7-position are much sought after owing to their medicinal values as reported in literature.[26-32] We were also interested in the synthesis of 6-methoxy tetralone for this is yet another substrate that has importance in some pharmaceutical preparations.[33,34,35] Parish and co-workers have substantial contribution in the area of steroidal oxidations.[36,37] Their works show that **PCC** can be modified to show selectivity for the oxidation of allylic alcohols in steroidal systems. Additionally, it was observed that in contrast to chromate oxidations of saturated alcohols in rigid systems, quasiequatorial allylic alcohols were oxidized faster than axial ones. Parish's work also involved examination of several other aromatic amines for the ability to promote allylic selectivity. 2,2′-Bipyridine, pyrazine, *s*-triazine and 2,4,6-triphenylpyridine were all tested in their reactions with the results showing that all the amines had some effect, but their appeared to be substrate dependent.[38] However, a combination of **PCC** with benzotriazole was found to exhibit excellent selectivity for allylic alcohols.[39]

Due to the biochemical importance of the oxidation product of Δ^5- steroids as mentioned above, such oxidations have been adopted in many laboratories.[40-44] Unfortunately, there are a number of limitations in the existing methods especially owing to the use of a large amount of the oxidants, exceedingly long reaction times, occasional use of very expensive reagent and at times, unfavorable yields of the products. These points will be elaborated later in this Chapter.

This problem drew our attention at a juncture when a new chromium(VI) reagent, 3,5-dimethylpyrazolium fluorochromate(VI), **DmpzHFC**, $C_5H_8N_2H[CrO_3F]$, [45] was just developed in our laboratory as a companion of **PFC** but with some improved properties. What was observed precisely was that **DmpzHFC** possesses all good qualities that **PFC** has, and in addition the results of a few preliminary reactions indicated that the new reagent might work better in situations where **PFC**, **PCC** or similar reagents reacted sluggish.

Accordingly, it was decided to investigate the oxidations of Δ^5- steroids and 6-methoxy tetralene to demonstrate that the desired keto functionalities can be generated relatively easily in high yields in a shorter period of reaction time by using far less amount of the reagent compared to that used in the literature procedures. [40-44] This Chapter, which is indeed the concluding Chapter of the thesis, elaborates on the efficacy of the new chromium(VI) reagent in bringing about the proposed transformations. It may be necessary to mention that oxidations of a variety of alcohols, fused ring hydrocarbons and a few other substrates worked very well with **DmpzHFC** and the results were reported earlier as a part of another Ph.D thesis.[45]

EXPERIMENTAL SECTION

All the chemicals used were of reagent grade. The sources of the chemicals and solvents have all been already given in Chapter 2. Quantitative determination of elements was accomplished by the methods described in Chapter 2. The details of all the equipment used for physico-chemical studies are also provided in Chapter 2.

SYNTHESIS OF AND CHARACTERIZATION OF 3,5-DIMETHYL-PYRAZOLIUM FLUOROCHROMATE(VI)

The reagent, 3,5-dimethylpyrazolium fluorochromate(VI), $C_5H_8N_2H[CrO_3F]$, (**DmpzHFC**), could be easily prepared in excellent yield from the reaction of CrO_3 with aqueous hydrofluoric acid and 3,5-dimethylpyrazole in the molar ratio of 1:2:1. In the preparation of the reagent **DmpzHFC**, chromium(VI) oxide first reacted with F^- ion in an acidic medium to form fluorochromate(VI) ion, CrO_3F^-, which was then precipitated by the counter cation $C_5H_8N_2H^+$ ($DmpzH^+$), obtained by the addition of 3,5-dimethyl pyrazole ($C_5H_8N_2$) to the acidic (*c.f.* aq. HF) medium. The synthesis is depicted below:

$$CrO_3 + HF + Dmpz \xrightarrow[(1:2:1)]{} \mathbf{DmpzHFC}$$

The synthetic procedure is described below:

To a solution of 5.6 g (56 mmol) CrO_3 in 2.5 mL water prepared in a 100 mL polyethylene beaker, 5 mL (120 mmol) of 48% HF was added with stirring. An orange red solution was obtained. The reaction mixture was then cooled in an ice-bath (0-5 °C) and 5.6 g (58.33 mmol) of 3,5-dimethylpyrazole was added in parts

with stirring when an orange crystalline compound separated out. This was filtered under vacuum using a polyethylene funnel and washed with petroleum ether (3x10mL). It was then rapidly dried in a vacuum desiccator and finally stored in a sealed polyethylene bag in a freezer. The isolated yield of the compound was found to be 11.6 g (92%) and melting point was recorded to be 56°C.

The compound analyzed very well with the experimental*ly* obtained values matching well with those of the calculated ones: Cr, 24.35 %; F, 8.95 %; C, 27.80 %; N, 12.98 %; H, 3.91 % (calculated : Cr, 24.06 %; F, 8.80 %; C, 27.78 %; N, 12.96 %; H, 4.21 %). It was soluble in dichloromethane and highly soluble in acetonitrile, chloroform, ethanol, methanol and acetone. Though the compound had limited stability at room temperature (25 °C), **DmpzHFC** was stable for a period of two months when stored at *ca.* 0 °C. The solution electrical conductance recorded using acetonitrile as solvent gave a value of 107 $\Omega^{-1}cm^2mol^{-1}$. The compound was diamagnetic and EPR silent. The IR spectrum of 3,5-dimethylpyrazolium fluorochromate exhibited bands at 954(s), 921(s) and 633(m) cm^{-1} assignable to $\nu_{as(Cr\text{-}O)}$, $\nu_{s(Cr\text{-}O)}$ and $\nu_{(Cr\text{-}F)}$ modes, respectively.[46] Additional bands in 800-1600 cm^{-1} region owed their origin to 3,5-dimethylpyrazolium cation $[C_5H_8N_2H]^+$.[47-49] The electronic absorption spectrum of the compound $C_5H_8N_2H[CrO_3F]$ in dichloromethane exhibited three bands at 27,701 cm^{-1} (ε=1,641$M^{-1}cm^{-1}$), 36,765 cm^{-1}(ε=4,101 M^{-1} cm^{-1}) and 46,296 cm^{-1}(ε=9,706 $M^{-1}cm^{-1}$), of which the fist two bands were assigned to $^1A_1 \rightarrow {}^1E$ and $^1A_1 \rightarrow {}^1A_1$ transitions, respectively, while the third band above 40,000 cm^{-1} was assigned to $^1A_1 \rightarrow {}^1E$ transition, which was typical of C_{3v}

symmetry of oxofluorochromium(VI) species.[50-52] The peak positions matched well with those reported for oxofluorochromium(VI) complexes thereby making further elaboration redundant.

OXIDATIVE TRANSFORMATIONS USING DmpzHFC

Oxidation of Δ^5-Steroids. A Typical Procedure.

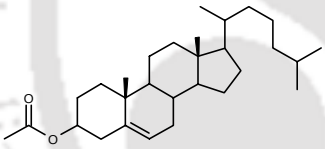
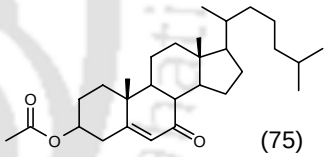
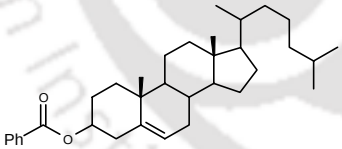
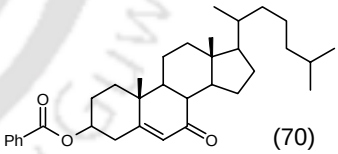
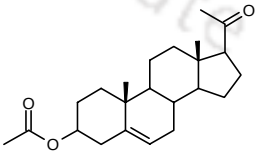
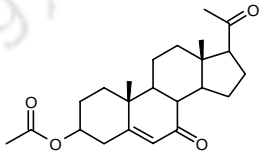
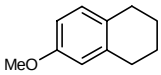
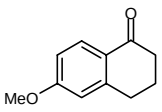
An amount of 0.43 g (1 mmol) 3-acetoxy-cholesterol was dissolved in anhydrous CH_3CN (10 mL) containing molecular sieves (0.020 g, type 3Å). 1.3 g (6 mmol) of **DmpzHFC** was added to the substrate and the mixture stirred under reflux for 10 h. The progress of the reaction was monitored by thin layer chromatography. Diethyl ether (50 mL) was then added to the reaction mixture, the ether layer decanted and the residue was further washed with ether (3x30 mL). The combined ether layers were passed through a short pad of Celite® to trap the reduced chromium. The ethereal solution was evaporated and the crude material subjected to column chromatography over silica gel using ethyl acetate: hexane (1 : 20) to afford 3-acetoxy-7-keto-cholesterol in 0.3 g (75%) yield as a white crystalline compound having m.p. 155-156 °C. (lit. m.p. 157-159 °C).[53]

Oxidation of 6-Methoxy Tetralene

An amount of 1 mmol (162 mg) of 6-methoxy tetralene was dissolved in 10 mL of anhydrous CH_3CN containing molecular sieves (0.020 g, type 3Å). 6 mmol (1.296 g) of **DmpzHFC** was added and the reaction mixture stirred under reflux conditions for 10 h. The progress of the reaction was monitored by thin layer

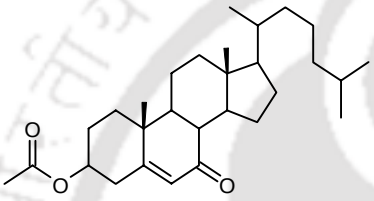
chromatography. Diethyl ether (50 mL) was then added to the reaction mixture, the ether layer decanted and the residue further washed with ether (3x30 mL). The combined ether layers were passed through a short pad of Celite® to trap the reduced chromium product. The ethereal solution *was* evaporated and the crude material subjected to column chromatography over silica gel using ethyl acetate: hexane (10: 90) to afford 6-methoxy-tetralone as a white solid in 60% yield (0.105 g) having melting point 78 °C (lit. m.p. 77-79 °C). [54]

Table 5.1. Oxidation of the Chosen Organic Substrates with **DmpzHFC**

substrate	solvent/ time (h)	substrate: oxidant	product / yield (%)
	CH_3CN/ 10	1:6	 (75)
	CH_3CN/ 10	1:6	 (70)
	CH_3CN/ 12	1:6	 (60)
	CH_3CN/ 10	1:6	 (60)

CHARACTERIZATION OF THE OXIDIZED PRODUCTS

The compounds were characterized by ^{1}H NMR and IR spectral techniques (Figures 5.1 – 5.8), along with melting point measurements. Characteristic IR and ^{1}H NMR data for the oxidized products are summarized as follows:

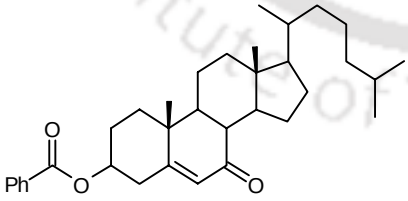


Name 3-Acetoxy-7-keto-cholesterol

M.p. 155 - 156 ^{o}C

IR(KBr) 1741, 1671 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.7 (s, 1H, -CO-C*H*=), 4.68 (m, 1H, -C*H*OCOCH$_3$), 2.05 (s, 3H, -OCOC*H*$_3$), 1.2 (d, 3H, -C*H*$_3$), 0.95 (s, 3H, -C*H*$_3$), 0.90 (s, 3H, -C*H*$_3$), 0.78 (d, 6H,-C*H*$_3$)

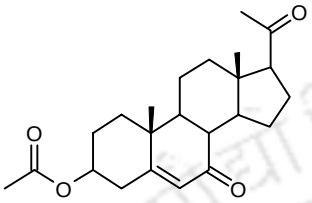


Name 3-Benzoyloxy-7-keto-cholesterol

M.p. 145 ^{o}C

IR(KBr) 1718, 1665 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 2H, Ar*H*), 7.47 (m, 3H, Ar*H*), 5.72 (s, 1H, -CO-C*H*=), 5.01 (m, 1H, -C*H*OCOAr), 1.25 (d, 3H, -C*H*$_3$), 0.98 (s, 3H, -C*H*$_3$), 0.92 (s, 3H, -C*H*$_3$), 0.73 (d, 6H, -C*H*$_3$)

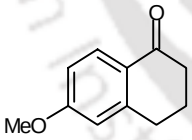


Name 7-keto-pregnonalone acetate

M.p. 121-122 ^{o}C

IR (KBr) 1741, 1671 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.6 (s, 1H, -CO-C<u>H</u>=), 4.68 (m, 1H, -C<u>H</u>OCOCH$_3$), 2.08 (s, 3H, -OCOC<u>H</u>$_3$), 2.05 (s, 3H, -COC<u>H</u>$_3$), 1.00 (s, 3H, -C<u>H</u>$_3$), 0.98 (s, 3H, -C<u>H</u>$_3$)



Name 6-Methoxy-1-tetralone

M.p. 78 ^{o}C

IR (KBr) 1671, 1598 cm^{-1}

^{1}H NMR. (300 MHz, $CDCl_3$): δ 7.99 (d, 1H, Ar<u>H</u>), 6.80 (d,1H, Ar<u>H</u>), 6.72 (s, 1H, Ar<u>H</u>), 3.84 (s, 3H, ArOC<u>H</u>$_3$), 2.87 (t, 2H, ArCOC<u>H</u>$_2$-), 2.55 (t, 2H, ArC<u>H</u>$_2$-), 2.12 (m, 2H, ArCH$_2$C<u>H</u>$_2$-)

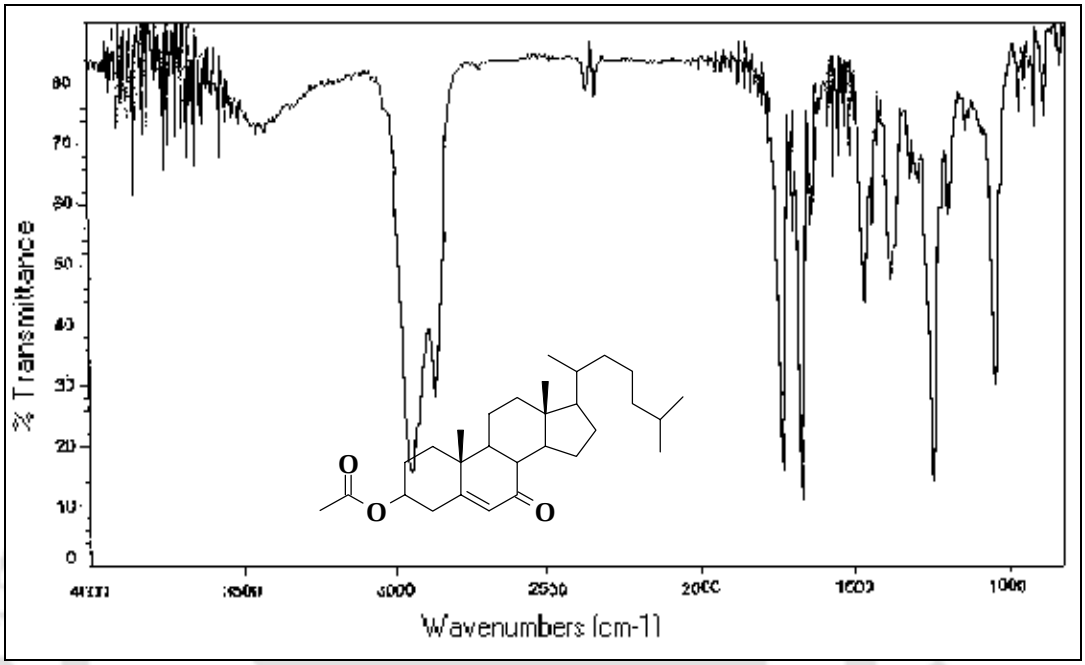


Figure 5.1 IR spectrum of **3-Acetoxy-cholest-5-ene-7-one**

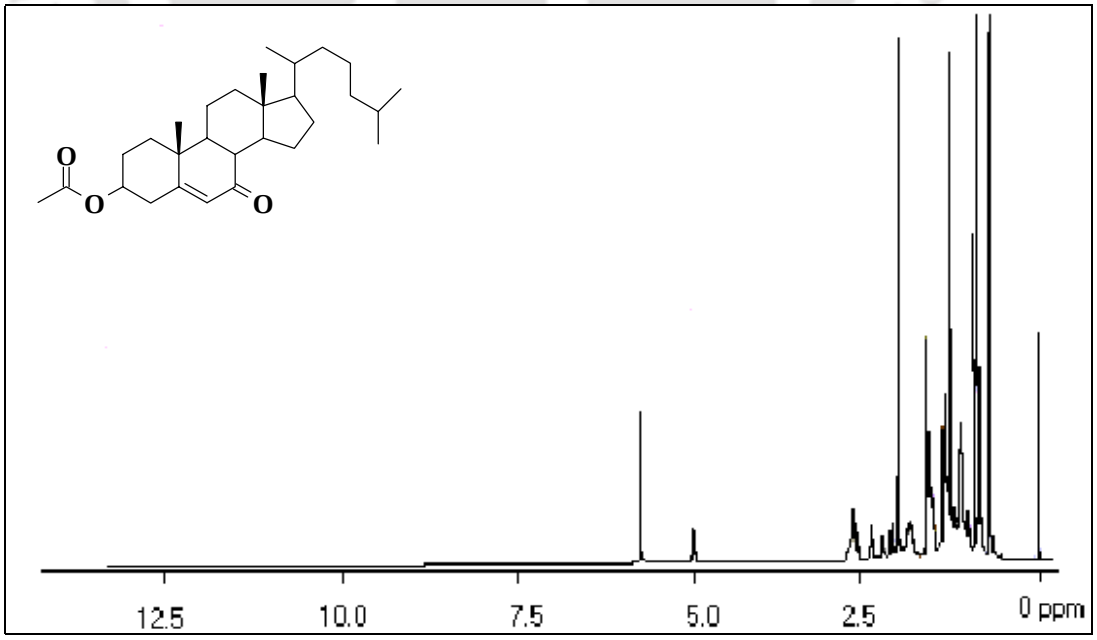


Figure 5.2 ^{1}H NMR spectrum of **3-Acetoxy-cholest-5-ene-7-one**

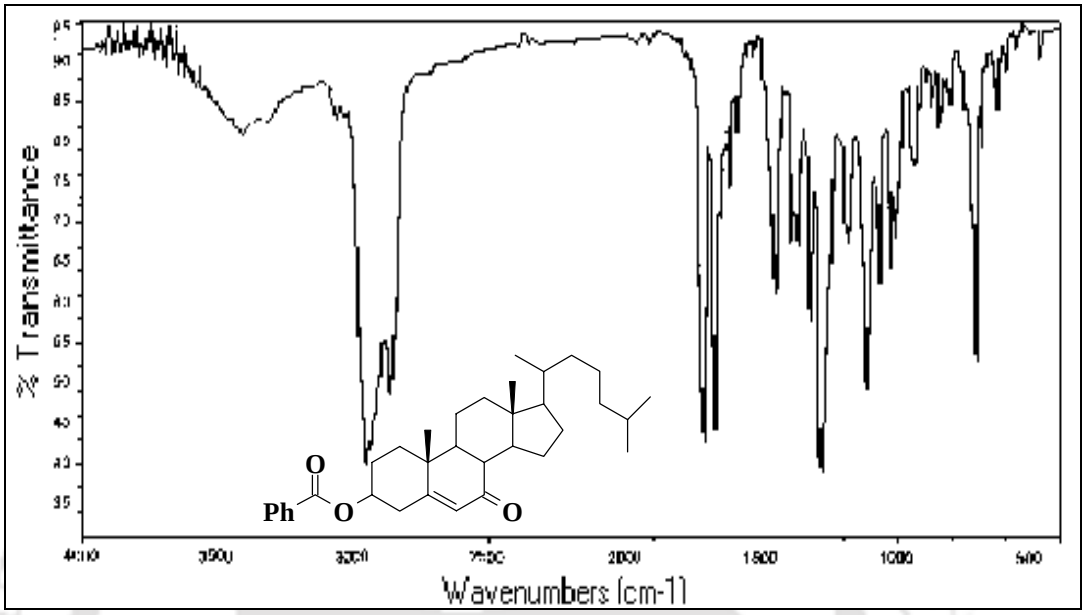


Figure 5.3 IR spectrum of **3-Benzoyloxy-cholest-5-ene-7-one**

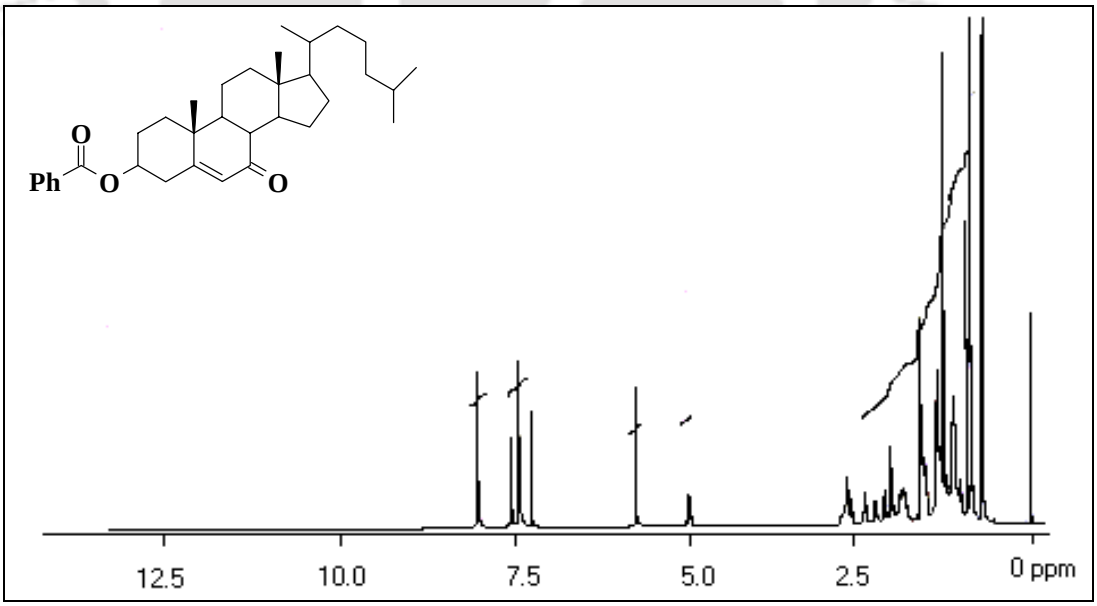


Figure 5.4 ^{1}H NMR spectrum **3-Benzoyloxy-cholest-5-ene-7-one**

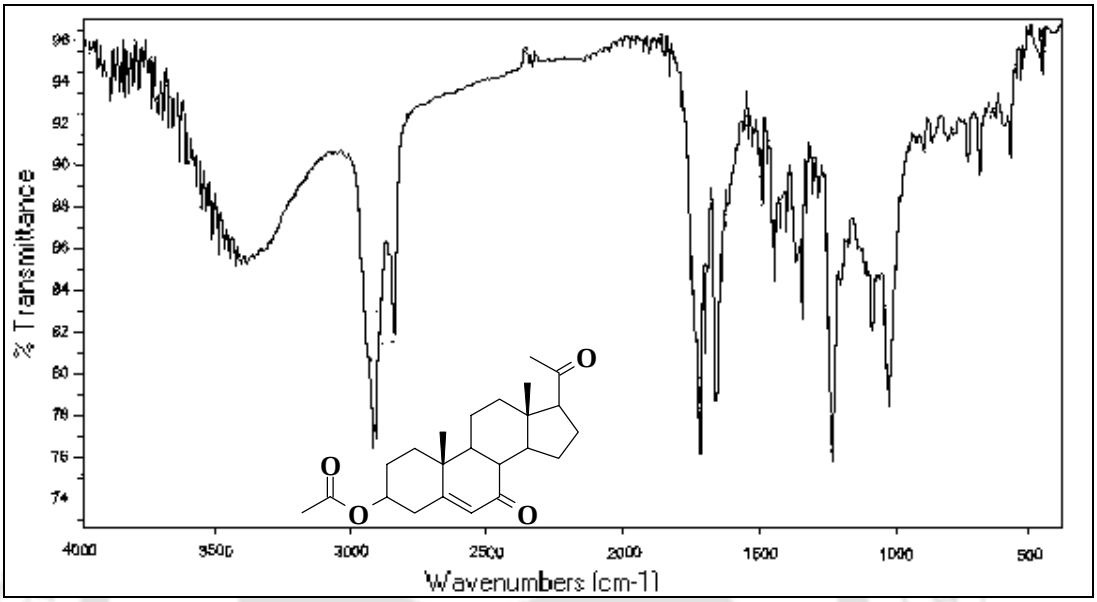


Figure 5.5 IR spectrum of **7-Keto-pregnonalone acetate**

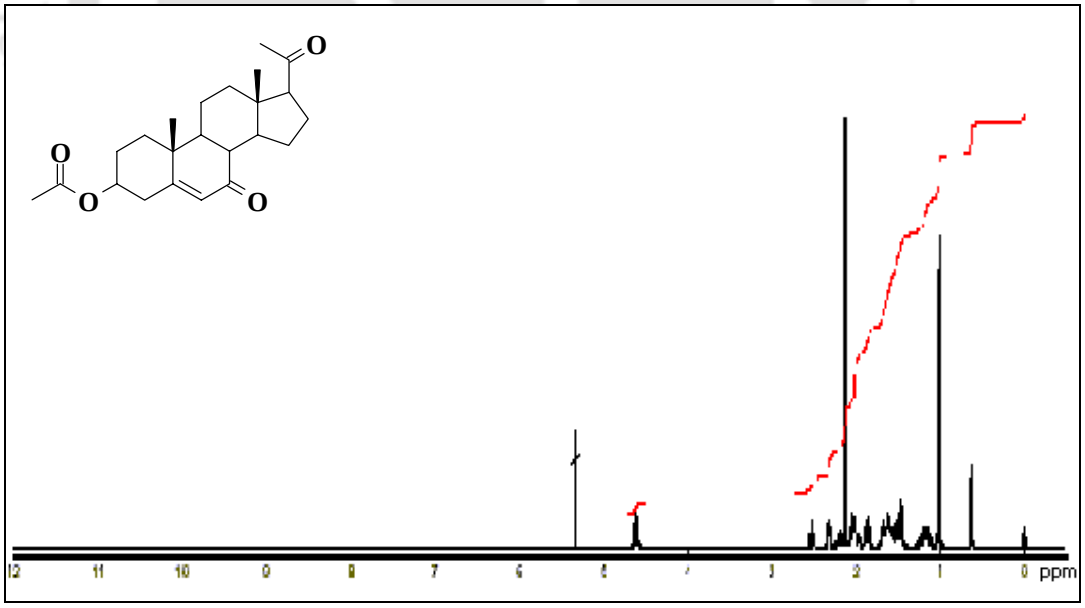


Figure 5.6 ^{1}H NMR spectrum of **7-Keto-pregnonalone acetate**

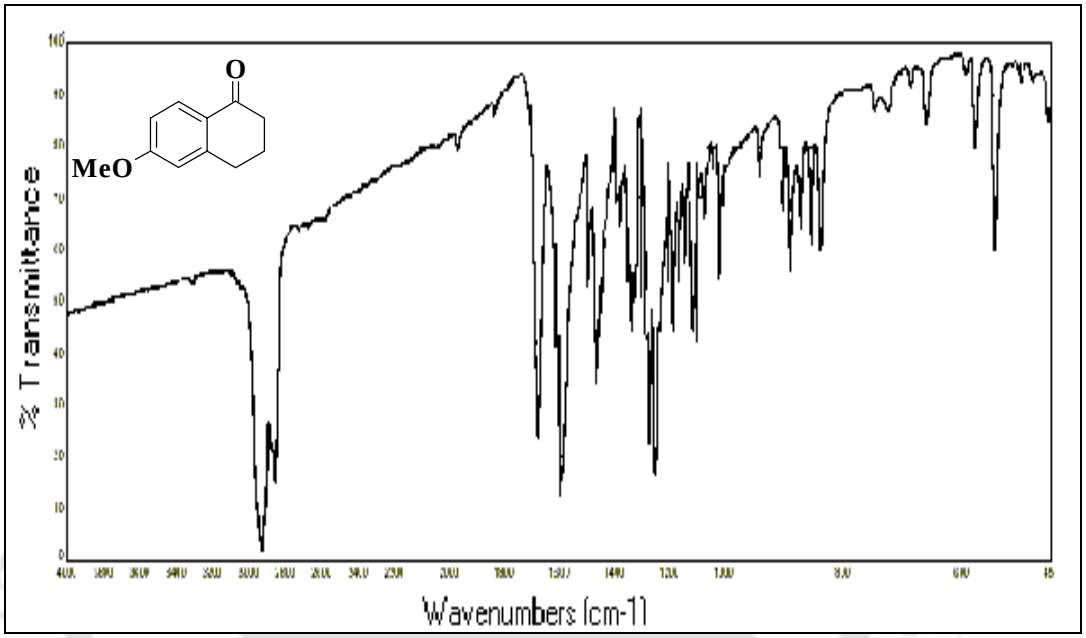


Figure 5.7 IR spectrum of **6-Methoxy tetralone**

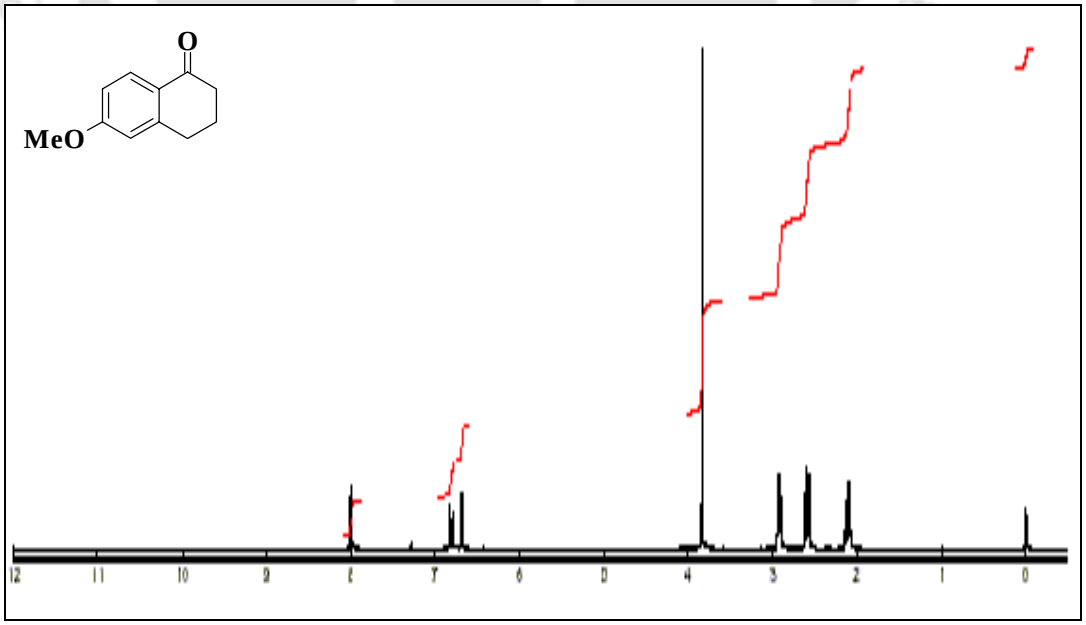


Figure 5.8 ^{1}H NMR spectrum of **6-Methoxy tetralone**

RESULTS AND DISCUSSION

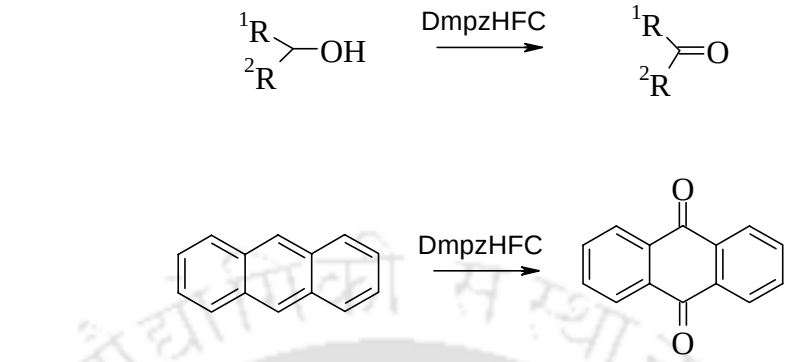
As an element fluorine behaves quite different from the rest of the members of the group (i.e., Cl_2 through I_2). Some of these differences are attributed to its (F_2) low dissociation energy, relatively high bond strength of F–metal or F–nonmetal bonds, relatively small size of the fluorine atom or fluoride ion, and above all the highest electro negativity of the element. The ion F^- interacts very well with higher valent transition metals and makes relatively stable coordination. And thus fluoride coordination to a highervalent metal centre renders it more electrophilic or in other words the oxidation profile becomes superior. This perhaps was one of the prime reasons behind the development of pyridinium fluorochromate (**PFC**), $C_5H_5NH[CrO_3F]$, at a juncture when pyridinium chlorochromate (**PCC**), $C_5H_5NH[CrO_3Cl]$, was already flourishing as a useful oxidant in organic synthesis. Then came the era of the next generation chromium(VI) reagents, *viz*., **PFC**,[15,17] to a good extent quinolinium fluorochromate (**QFC**), $C_9H_7NH[CrO_3F]$,[18] with the latest one in the series being dimethylpyrazolium fluorochromate, **DmpzHFC**, (DmpzH[CrO_3F]).

The hierarchy in the fluorochromates has been an outcome of our search for a qualitatively improved version of the fluorochromate reagent, which has now landed us up with DmpzH[CrO_3F], (**DmpzHFC**).

One of the notable drawbacks of the earlier chromium(VI) reagents (*c.f.* **PCC**) owes its origin to their higher acidity, often demanding the reaction medium to be buffered. Thus, the main concern for us was to develop a reagent that would not only have far controlled acidity but also be as effective, if not more, as **PCC** as an

oxidizing agent. This has been one of the driving forces behind the development of the fluorochromates(VI). Important in this context is that **DmpzHFC** appears to be relatively more basic compared to **PFC** and to **QFC**. Indeed a pH value of 4.9 (0.01 M aqueous solution) with the corresponding pK_a being 7.8 attests to its far less acidic character. Meanwhile, the pH of 0.01 M solutions of **PCC**, **PFC** and **QFC** were found to be 1.75, 2.45 and 3.35, respectively, with the corresponding pK_a values being 1.4, 2.7 and 4.7,[55] thereby rendering us to be certain that **DmpzHFC** is least acidic among the four mentioned herein. Another point of advantage of the reagent is its solubility. The solubility of the reagent in organic solvents has been found to be comparatively higher than **PFC**, **PCC** and **PDC.** **DmpzHFC** is soluble in dichloromethane and highly soluble in acetonitrile, chloroform, ethanol, methanol and acetone.

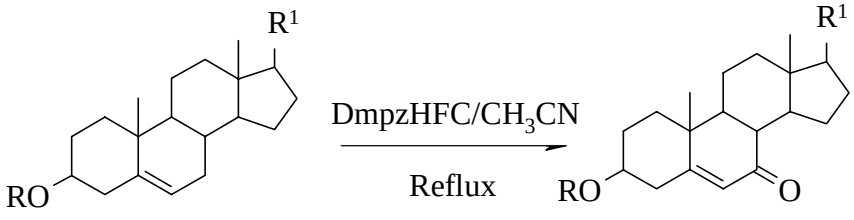
In order to establish the efficacy of the reagent as an oxidant, a number of oxidative transformations were carried out on a wide array of substrates. The results showed that **DmpzHFC** readily oxidizes primary and secondary alcohols to their corresponding aldehydes and ketones, fused ring hydrocarbons such as anthracene and phenanthrene to 9,10-anthraquinone and 9,10-phenanthraquinone, respectively, (Scheme 5.1) and triphenylphosphine to triphenylphosphine oxide in high to very high yields.



Scheme 5.1 Oxidation of Alcohols and Polycyclic Arenes by DmpzHFC

The results of these investigations have been highly encouraging. It may be noted that most of the transformations mentioned above formed a part of another thesis,[45] and hence no further discussion is made here. However, it must be confessed that these reactions were necessary to carry out before proceeding further because the results would guide the next course of action. Indeed, the knowledge obtained from the studies provided cues for a set of transformations that follows.

Going by the observed reactions profiles and the inherent properties of **DmpzHFC**, it was applied to the much sought after allylic oxidations. What has been now found is that the reagent is very effective for the oxidation of Δ^5- steroidal systems (Table 5.1), (Scheme 5.2) to the corresponding α,β-unsaturated ketones.



Scheme 5.2 Δ^5-Steroidal Oxidations

In all the cases described herein, the products were obtained in moderate to high yields (*vide* Experimental). Significantly, Δ^5- steroids are more than mere probes for oxidation since Δ^5- steroids with a ketone function at C-7 (Δ^5-7-ketones) are found in animal tissues[31] and food stuffs[32] and are also known to be inhibitors of mammalian sterol biosynthesis[26-28] and cell replication.[29,30] Though such oxidations are not unprecedented in the literature as mentioned earlier in this Chapter, the allylic oxidations of Δ^5- systems carried out with chromic acid reagents[40], **PCC**,[41] **PDC**[42] and **$RuCl_3$-TBHP**[43] had unfortunately only limited success, had involved prohibitively expensive reagent or had required a large excess of the reagent (1:25 - 120, substrate: oxidant), stringent reaction conditions and a longer reaction time. Thus, for instance, an amount of 25 - 30 molar equivalents of **PCC** in refluxing dichloromethane required 48 h to afford ca. 55 % yield of the product.[41] Likewise, a reaction time of 24 h was reported to be needed for similar oxidations involving 25 molar equivalents of **PCC** or **PDC** in refluxing benzene or dimethyl sulfoxide, or pyridine at 100 °C.[42] In so far as **$RuCl_3$-TBHP** oxidation of Δ^5- steroids is concerned, it is not only that the reagent is expensive with the oxidation procedure being tedious but also that the reaction time is much longer (typically *ca.* 30 h) compared to the present protocol. Importantly, it has now been demonstrated through this work that only a six molar equivalent of **DmpzHFC** in dry acetonitrile afforded the desired products in very respectable yields in a comparatively much shorter time (i.e., 10 h). The narration may remain incomplete if it is not stated very clearly that Δ^5- steroidal oxidations involving one of our previously developed reagents, **PFC**,

($C_5H_5NH[CrO_3F]$) has not provided very promising results in solution state reactions so far.

In yet another example, 6-methoxy-tetralene, a very good case of an activated hydrocarbon, has been oxidized to 6-methoxy-1-tetralone as a case of ketone formation at the C-1 position. Incidentally, this product appears to be the key building block for several life-saving drugs and steroid molecules.[33-35] Notable here again is that the reaction time in the present case has been relatively short (10 h) with the molar equivalent of the reagent/ oxidant required being far less (6 equivalent) compared to the literature procedures (13-48 h, 60-120 equivalents).[41,44]

In order to have an insight into the mechanism, the chromium species was isolated after oxidation as a brown microcrystalline product. From the results of chemical analyses, chemical determination of the oxidation level of the metal (3.9-4.1), magnetic susceptibility (μ_{eff} = 2.92 BM at RT) and EPR (single line at g = 1.935 $\pm$ 0.005) measurements in addition to IR spectroscopy, it has been ascertained that the product is a chromium(IV) species, $C_5H_8N_2H[CrO_2F]$. This suggests very clearly that **DmpzHFC** serves as a 2-electron transfer agent.

CONCLUDING REMARKS

Since partial oxidations of organic substrates and the use of chromium(VI) reagents to bring about such oxidative transformations under mild conditions are inevitable, search for more and more efficient reagents based on Cr(VI) will continue. The new reagent **DmpzHFC**, which is an improved version of many of its

predecessors, has a number of advantages over its companion reagents like **PCC**, **PDC** and **PFC** or **$RuCl_3$-TBHP** as evident from the consideration of the amount of the reagent required for a large variety of oxidations, solubility in different solvents, controlled acidity, shorter reaction time and high to very high yields of products. The reduced chromium species can be trapped on a silica gel or Celite® column for safe disposal or land filled.

Many of the partial oxidations, if not all, may proceed with alacrity involving **DmpzHFC** under solvent-free conditions by either simply grinding them together at room temperature or in some cases followed by heating at a relatively higher temperature. It is anticipated that the reactions beginning with solid-solid interactions may proceed far more rapidly by the intervention of a liquid phase arising due to the existence of a lower melting eutectic formed by a combination of the product and the reagent. It is perceived that a liquid or melt phase may imbue the individual molecules with a required mobility for productively important reactive collisions which in turn may intervene allowing for rapid reactions to take place between the two solid reactants (substrate and reagent). The investigation of solvent-free reaction chemistry is topically important especially in terms of 'green chemistry' culture. It is anticipated that solvent-free chemistry is going to take over the corresponding solution phase counter-part both in laboratory as well as industrial scale production of chemical products, at least in a large measure.

Based on the results hitherto obtained, as well as those anticipated, it may be stated that **DmpzHFC** is an important addition to the existing toolbox of oxidizing agents.

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