Macromolecular peroxo complexes of Vanadium(V) and Molybdenum(VI): Catalytic activities and biochemical relevance

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Abstract. Our recent achievements concerning the synthesis and characterization of water soluble peroxo complexes of V(V) and Mo(VI) in macroligand environment, as well as some key features of biological relevance of these compounds, such as their hydrolytic stability, activity with phosphohydrolase enzyme vis-à-vis free peroxovanadium (pV) or peroxomolybdenum (pMo) complexes, and their activity in biomimetic oxidative bromination are presented here. Immobilization of pMo species on insoluble polymer matrices *viz.*, amino acid functionalized Merrifield resins and poly(acrylonitrile) on the other hand, afforded a set of heterogeneous catalysts highly effective in facile organic transformations such as selective oxidation of organic sulfides and oxidative bromination of aromatic substrates by H₂O₂, at ambient temperature. The methodologies are straightforward, high-yielding, halogen-free and the catalysts afford easy regeneration. Our findings illustrate the various features which make the procedures sustainable and synthetically useful.

Keywords. Macromolecular metal complexes; peroxovanadates; peroxomolybdates; enzyme inhibitors; polymer-supported metal catalysts; bromoperoxidases.

1. Introduction

Vanadium has a chemical versatility that is useful to biological systems^{1–7} and is redox active under physiological conditions.^{8,9} One of the most fascinating domains of vanadium chemistry is its peroxo chemistry.^{1,3,10–15} It has been appreciated for at least 140 years that characteristic colour reactions may occur when hydrogen peroxide is added to solutions of transition metal derivatives.¹⁶ Among the various d⁰ transition metal peroxo systems, V(V), Mo(VI) and W(VI), which have clear structural and isoelectronic relationships, attract continuous research attention because of their versatility and selectivity as stoichiometric or catalytic oxidizing or oxo-transfer agent in a variety of organic oxidations such as epoxidation of alkenes,^{17–20} oxidation of sulfides and sulfoxides,^{21–26} primary and secondary alcohols,^{27,28} as well as halide oxidation.^{29–32} Besides these, the active involvement or relevance of these peroxometallates in haloperoxidase,^{29,31,32} their insulino-mimetic,^{33–36} anti-neoplastic³⁷ and enzyme inhibitory activity^{38,39} have been well documented. The vanadium-dependent bromoperoxidase (V-BPO) is now the subject of tremendous interest for chemists as well as biologists. Studies on synthetic models of V-BPO have been extremely useful in helping to unravel

details of the structure and mechanism of activity of the enzyme.^{1,6,30,40}

Vanadium and its compounds including peroxovanadates (pV) have strong influences, inhibiting the function of a large number of enzymes and promoting the function of others.^{7,41,42} Peroxovanadates have been reported to affect cellular signaling by influencing the functioning of a number of enzymes including mitogen-activated protein kinase (MAPkinase), tyrosine phosphatases, phospholipase D.^{7,43,44} It has been suggested that the inhibitory action of vanadate and pV on protein phosphatase hydrolysis may be an important part of their insulin-like effect.^{35,45} Enzyme inhibition has already been identified as an important pathway for the action of inorganic drugs and remains an area needing further exploration.⁴⁶ Apart from peroxovanadates (pV), molybdate and peroxomolybdate (pMo) as well as tungstate and peroxotungstate (pW) have also been reported as potential insulin mimics with an ability to inhibit the activity of phosphoproteins.⁴⁷ These fascinating findings led to a resurgence of interest in these systems.^{10,47,48}

Out of the myriad synthetic heteroligand pV compounds tested for various biochemical activities, majority have been found to suffer from the drawback of being hydrolytically unstable and toxic,^{42,49} which limits their clinical potential. Therefore, the quest for new biologically effective pV compounds, with greater

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stability and low toxicity continues unabated. In contrast, although ample evidences exist to show that pMo and pW species exhibit superior bio-relevant characteristics *viz.*, stability, bioavailability and low toxicity,^{47,50} these peroxometallates have received scant attention as biologically active agents.

In our recent work, we have focused on immobilizing peroxometal (pM) compounds on water soluble, as well as insoluble polymer supports anticipating that a macroligand environment will add advantages of polymeric reagent such as stability and enhanced oxidant activity to the potential ability of the active pM species. Polymers usually being devoid of some of the unfavorable properties of monomeric species, such as lability, volatility, toxicity and odour,⁵¹ are likely to add extra benefits to such systems. Our efforts have been directed towards two major goals: (i) to develop efficient catalysts for organic oxidations, effective under environmentally clean reaction conditions, and (ii) to generate peroxometallates with biologically important attributes. There has been a continuous upsurge in interest in metal containing polymeric materials in general, due to their tremendous potential in diverse fields like catalysis, liquid crystals, biosensors, drug delivery systems and a host of other biomedical applications.^{52–56} It is apparent after reviewing the literature that although a few peroxometal systems^{20,57–60} including pV and pMo compounds,²⁰ supported on insoluble cross-linked polymers were prepared recently which were reported to exhibit good activity as catalytic or stoichiometric oxidant in organic oxidations, none of the water soluble polymers (WSP) have been explored for use as polymeric support to obtain peroxo metal species in macroligand environment.

In this article, we present a summary of our findings on biochemical as well as catalytic activities exhibited by pV and pMo containing macromolecules synthesized in our laboratory, in recent years. We have generated a series of polymer-bound complexes by anchoring peroxo species of V(V), Mo(VI) or W(VI) to pendant functional groups of WSPs,^{61–63} as well as insoluble polymer resins.^{64–66} Interestingly, the soluble macrocomplexes exhibited unique oxidant activity as well as biochemical properties including anti-bacterial⁶¹ and enzyme inhibitory activities.^{62,63} Significantly, immobilization of the pV and pMo species enhanced their stability as well as their ability to resist degradation under the effect of the enzyme catalase.^{61,62} Most notable finding of our study was that the polymer anchored and neat peroxo compounds induced their inhibitory effects on ALP via distinct mechanisms.^{62,63} Moreover, polymer bound pV⁶¹ and pW complexes⁶⁵ efficiently mediated oxidative bromination of organic substrates under

mild condition at near neutral pH, considered as essential requirement of a biomimetic model. It was observed that even a minor change in co-ordination environment around the peroxometal moieties in the polymeric complexes could alter their bioactivity as well as their catalytic activity tremendously.⁶¹ In view of these interesting findings, anchoring of peroxometallates to WSPs has recently been recognized as a promising new field.¹⁰

Furthermore, a set of new heterogeneous catalysts have been developed by immobilization of pMo species on insoluble polymer supports *viz.*, amino acid functionalized Merrifield resins⁶⁶ and poly(acrylonitrile).⁶⁵ The catalysts exhibit excellent activity, stability and selectivity for oxidation of thioethers and dibenzothiophene (DBT) to the corresponding sulfoxides by 30% H₂O₂, one of the most sustainable oxidant, at ambient temperature.⁶⁶ In addition, a pair of pMo and pW compounds supported on poly(acrylonitrile) matrix heterogeneously catalyzed oxidative bromination of range of activated aromatic substrates with H₂O₂⁶⁵ under ecologically acceptable reaction conditions. These interesting features highlight the synthetic value of the catalytic protocols.

2. Metals and metal complexes bound to macromolecules – general aspects

Metal containing macromolecules in general, constitute a fascinating field of science.^{52,67} It is readily understandable that materials with unusual properties are obtained by having a metal as part of a macromolecule.⁶⁸ Anchoring of an active transition metal complex to a functionalized polymer is interesting from the view point of designing effective catalysts as well as modelling of complex biomolecules and bioprocesses. Various combinations of metal complexes or metals with organic, inorganic and semi-organic macromolecules exist.⁶⁹ Diverse approaches to prepare polymer supported complexes as well as a variety of names for supporting processes such as immobilization, anchoring, attachment and “heterogenization of homogeneous complexes” have been proposed.⁷⁰ According to the Wohler’s classification,⁷¹ a metal complex or metal can be part of a macromolecular chain or network in several ways. “**Macromolecular metal Complexes**” (**Type I**) are formed when a metal ion, a metal complex or metal chelate is attached to a linear or cross-linked organic polymer via a covalent, a coordinative (at the metal), a complex (at the ligand of the complex), an ionic or π -type bonds (figure 1). In a “**ligand macromolecular complex**” ligand of a metal complex constitutes a part of a linear or cross-linked macromolecule (**Type II**). On the other hand, in “**metal macromolecular**

Figure 1. Schematic model of binding of metal ion, metal complexes or π - π complexes at macromolecular carriers.⁷¹ Copyright (2005) From Ref. ⁷¹. Reproduced by permission of Taylor and Francis Group, LLC, a division of Informa plc.

complexes” (Type III), metals exist as part of a linear chain or network. Physical incorporation of metals or metal clusters in macromolecular environment to form **“macromolecule incorporated metal complexes” (Type IV)** can provide an access to new composite materials, which is an emerging field of research.

Different polymeric materials, natural and synthetic, prepared both by addition and condensation polymerization are reported as matrices to anchor complexes.⁷² In the case of linear or branched organic polymers, the macromolecular metal complexes are soluble in organic solvents and their structure can be identified rather easily. The bridged macromolecular metal complexes are more stable, have less defined structure and are less soluble. The complexes with intermolecular bridge bonds are insoluble and difficult to characterize.

The reaction of appropriate polymers and reagents with catalytically active groups often confers activity to the polymer and generates a functional polymer.⁷⁰ The catalytic properties of immobilized metal complexes are controlled by a number of factors such as the nature and distribution of attached transition metal ions and the character of the polymer support, along with unreacted functional groups of the polymer after fixation and activation of metal complexes.⁷² Depending on the chemical nature of initial components, immobilized complexes can be soluble or insoluble in the reaction mixtures. Therefore, it is possible to transform homogeneous into heterogeneous catalysts and vice versa, which is a remarkable feature of such systems.⁷² In fact, immobilized catalysts combine the main features of homogeneous, heterogeneous and enzymatic catalysts such as high activity and selectivity, specific character and stability in operation which enhances their efficiency.⁷⁰ Recent progress in the field of biomimetic catalysis has amply demonstrated that immobilized complexes can be considered as models of biological catalysts because they can carry out multi-centre activation of a substrate like the metal enzyme.⁷³ The polymer bound metal complexes were shown to act as models for several metalloenzymes including catalase,

peroxidase, cytochrome P₄₅₀, myoglobin, hemoglobin, vitamin B₁₂, proteolytic and other enzymes.^{70,72} There are many heterogenized enzymatic systems, obtained by immobilization of catalase on synthetic polymers, which decompose H₂O₂ to H₂O and O₂.⁷²

3. Metal complexes anchored to water soluble polymers (WSP)

One of the significant features of a soluble polymer supported reagent is the facility of product synthesis and characterization afforded by the soluble support due to the advantages of homogeneity offered by it.^{74,75} The utility of water soluble macromolecular metal complexes in diverse fields including separation processes,^{76,77} biomedical^{78,79} and environmental applications^{67,68} are increasingly being recognized in recent years. Since water is the basic solvent for natural macromolecules, coordination compounds of metal ions with soluble macromolecular ligands find relevance in designing biomimetic models^{68,80} as well. The most important requirements for practical application of these polymers include: high hydrophilicity, an easy and cost effective route of synthesis, an adequate molecular weight distribution, chemical stability and high affinity to bind metal ions.⁵² The water soluble polymers are essentially polychelators with functional groups able to form co-ordinate bonds with metals.⁵² There are various types of soluble polymers bearing different functional groups available which are used as support for metal anchoring.⁷⁵ The commonly occurring ligands in these polychelators include amines, carboxylic acids, amides, alcohols, amino acids, pyridines and thiourea.⁵²

Use of WSP in catalysis is relatively a newer concept.⁶⁸ In fact, transition metal complexes attached to soluble non-cross-linked polymer is essentially a homogeneous catalyst with macromolecular ligands. The first example where a soluble polymer was used as an alternative to a cross-linked insoluble polymeric resin to support a chiral ligand, was reported in 1976

by Bayer and Schurig.⁸¹ An important progress in soluble polymer support occurred with the report of Janda and co-workers on supported chiral catalysts for asymmetric dihydroxylation of olefins, in the year 1996.⁸² Among the various types of soluble polymers, poly(ethylene glycol) (PEG) and non-cross-linked polystyrene are some of the most often used examples in the preparation of soluble polymer-supported catalysts.⁷⁵

The use of water soluble polymer-metal adducts opened new strategies in the development of pharmaceutical formulations and other biological applications.⁸³ Binding of active drug molecules to water-soluble polymeric drug carriers offer various advantages including improved drug pharmacokinetics, lower toxicity to healthy organs, possible facilitation of preferential uptake by targeted cells and programmed drug release profile.^{84,85} A remarkable improvement has been achieved in case of platinum based anti-cancer drugs by anchoring it to soluble polymers.⁸⁵ Such polymer-drug conjugates can increase the effectiveness of an anti-cancer drug compared to their low molecular weight analogue. In view of these advancements, it appears likely that metal containing polymers would be a rich source of potential future therapeutic agents.

4. Peroxo compounds of vanadium and molybdenum anchored to WSP

4.1 Synthesis and characterization

The task of constructing metal containing macromolecules that are stable, active as well as selective with respect to a specific property obviously requires adequate consideration particularly with respect to choice of the macroligand. We have selected for our study, a set of macroligands, known to serve as effective chelators leading to stable metal ligand linkage.⁵² Most importantly, each of the selected polymers are chemically stable, commercially available or can be prepared easily and are relatively cheaper.⁶¹ The additional attractive attributes of the polymers are their biocompatibility as evident from their use in different biomedical applications such as in bioadhesive products, drug delivery and anti-microbial activity.⁸⁶

We have prepared a series of polymer bound peroxo complexes of vanadium(V) and molybdenum(VI) of the type, $[V_2O_2(O_2)_4(\text{carboxylate})]-PA$ [$PA = \text{poly}(\text{sodium acrylate})$] (**PV₁**), $[VO(O_2)_2(\text{carboxylate})]-PMA$ [$PMA = \text{poly}(\text{sodium methacrylate})$] (**PV₂**), $[VO(O_2)_2(\text{sulfonate})]-PSS$ [$PSS = \text{poly}(\text{sodium 4-styrene sulfonate})$] (**PV₃**), $[V_2O_2(O_2)_4(\text{carboxylate})VO(O_2)_2(\text{sulfonate})]-PSSM$

[$PSSM = \text{poly}(\text{sodium styrene sulfonate-co-maleate})$] (**PV₄**), $[Mo_2O_2(O_2)_4(\text{carboxylate})]-PA$ [$PA = \text{poly}(\text{sodium acrylate})$] (**PMo₁**), $[MoO(O_2)_2(\text{carboxylate})]-PMA$ [$PMA = \text{poly}(\text{sodium methacrylate})$] (**PMo₂**), $[MoO(O_2)_2(\text{amide})]-PAm$ [$PAm = \text{poly}(\text{acrylamide})$] (**PMo₃**), by reacting V_2O_5 (for compounds **PV₁**, **PV₂**, **PV₃** and **PV₄**) or H_2MoO_4 (for **PMo₁**, **PMo₂** and **PMo₃**) with H_2O_2 and the respective water soluble macromolecular ligand at pH 5-6.^{61,62} In a solution of vanadate or molybdate and excess H_2O_2 at a pH ≥ 5 , formation of diperoxo species of these metals is favoured.^{16,87,88} We have observed that formation of the $[MO(O_2)_2]$ ($M = V$ or Mo) moieties and their coordination to the macroligands occurred optimally at near neutral pH.

On the basis of the results obtained from spectral (IR, electronic, ^{13}C NMR, ^{51}V NMR and ^{95}Mo NMR), TGA-DTG and SEM-EDX analysis the structures of the type shown in figure 2 a, b, d, e has been envisaged for the polymer anchored pV complex, **PV₁ – PV₄**.^{61,62} The results are also consistent with the proposed structures of the pMo containing macrocomplexes **PMo₁**, **PMo₂** and **PMo₃** presented in figure 2a–c.⁶²

The metal loading on the compounds, estimated on the basis of Energy Dispersive X-ray (EDX), atomic absorption spectroscopy (AAS) and elemental analysis data was found to vary within the range 2.1 (**PV₁**) to 0.7 (**PMo₃**) mmol g⁻¹ of polymer.^{61,62} The scanning electron micrographs of the polymer anchored complexes (figure 3) revealed that the metal ions are distributed across the surface of the polymers. The ^{51}V NMR spectra of **PV₁** and **PV₄** are presented in figure 4.⁶² In the spectrum of the compound **PV₁** a single major signal was found at -757 ppm owing to the polymer bound dinuclear peroxovanadium species which is within the range commonly observed for diperoxovanadate.^{10,89,90} The compound **PV₄**, showed two closely spaced peaks at -753 and -758 ppm [figure 4(b)]. These likely refer to complexation of the metal centres through two types of pendent ligand sites *viz.*, sulfonate and maleate carboxylate groups, available on the co-polymer matrix, poly(sodium styrene sulfonate-co-maleate) (**PSSM**). The ^{95}Mo NMR spectrum of **PMo₁** displayed a single resonance at -225 ppm (relative to $[MoO_4]^{2-}$) which is typical of monoperoxomolybdenum species.⁹¹

Hydrolytic stability being one of the most important conditions required to be fulfilled by metal complexes to be useful as therapeutic or bio-relevant agent,⁹² we considered it imperative to ascertain the stability of the title compounds in solution. The stability of water soluble polymer bound compounds, **PV₁–PV₄** and **PMo₁ – PMo₃** has been examined in solution of pH values

Figure 2. Proposed structures of polymer anchored compounds, (a) **PV₁** ($n = 3$) and **PMo₁** ($n = 1$), (b) **PV₂** ($n = 2$) and **PMo₂** ($n = 1$), (c) **PMo₃**, (d) **PV₃** and (e) **PV₄**. “~~~~” represents polymer chain.^{61,62} Reprinted from ref.⁶¹, Copyright (2008), with permission from Elsevier, reprinted with permission from ref.⁶². Copyright (2011) American Chemical Society.

in the range of 1.2 to 8.0. The evidences gathered by determining their peroxide content, monitoring the absorbances in the electronic, ^{13}C , ^{51}V and ^{95}Mo NMR spectra at specified time intervals, revealed that the compounds remain stable in solution of acidic as well as higher pH for at least 12 h.^{61,62}

4.2 Interaction with alkaline phosphatase (ALP)

Phosphate ester bond, an extremely important linkage within the living cell, participates in storage and transfer of the genetic information, carries chemical energy and regulates the activity of enzymes and signalling molecules in the cell.⁹³ Alkaline phosphatase (ALP) is a membrane bound zinc metalloenzyme with broad substrate specificity that catalyzes the cleavage of phosphate esters with an optimal activity at higher pH (>7.5).^{94,95} The ubiquitous enzyme has been used extensively in immunoassays.^{94,96}

The inhibitory effect of vanadate towards phosphatase was established in 1977 when Cantley and co-workers⁹⁷ reported that vanadate is a potent inhibitor of Na, K-ATPase. This was the beginning of understanding the potential of vanadate in enhancing effectiveness of a variety of phosphate esters, including phosphoproteins,

by inhibiting their hydrolysis. Earlier studies suggested that the inhibitory ability of different vanadium derivatives, including peroxovanadates, to modulate ALP activity depend on several factors such as oxidation state of the metal, co-ordination geometry, stability of the compounds under physiological conditions, and the nature of the phosphoproteins.⁴⁶ Apart from vanadate, other oxyanions viz., molybdate and tungstate^{98,99} are also known to induce competitive inhibition of ALP. The competitive inhibition of ALP by vanadate, molybdate and tungstate has been ascribed to the formation of pentaco-ordinated or hexaco-ordinated structures of these species, which are often described as phosphate analogues.^{98,99} Very little information however, is available pertaining to similar studies carried out on discrete pMo or pW systems.^{62,100–102} The majority of the synthetic pV compounds tested were competitive inhibitors of the enzyme although, there are examples of diperoxovanadate compounds showing mixed-inhibition.^{103,104} Pertinent here is to mention that our recent investigation on a series of monomeric and dimeric pW^{100,101} and pV^{100,102,105} complexes with amino acids and di- and tripeptides as ancillary ligands revealed that such compounds also exert mixed-type of inhibition on activity of ALP.

Figure 3. Scanning electron micrographs of (a) PSS, (b) PV_3 , (c) PSSM and (d) PV_4 . EDX spectra of (e) PV_3 and (f) PV_4 .⁶² Reprinted with permission from ref. ⁶². Copyright (2011) American Chemical Society.

As a direct sequel to our work on enzyme inhibitory activity of peroxo-metallates, we have investigated the effect of the pV and pMo macrocomplexes on the function of a mammalian ALP, vis-à-vis effect of neat pV or pMo complexes.^{62,100–102,105} We were specifically interested to know whether binding of low molecular weight peroxo metal species to macromolecular ligands would lead to an alteration of their affinity to inhibit enzyme function. Employing the established enzyme assay system and p-NPP as substrate, the *in-vitro* effect of the polymer anchored compounds $PV_1 - PV_4$ and $PMo_1 - PMo_3$ upon the activities of the membrane associated protein rabbit intestine ALP was examined and compared with the effect induced separately by the previously reported free diperoxometallates viz. $Na[VO(O_2)_2(H_2O)]$ (DPV), $[MoO(O_2)_2(glycine)(H_2O)]$ (DMo_1), $[MoO(O_2)_2(asparagine)(H_2O)]$ (DMo_2) and the respective oxyanion, vanadate or molybdate. The data presented in figure 5 demonstrate that the pV and pMo compounds irrespective of being free or immobilized,

efficiently inhibit the ALP activity in a dose dependent manner.

The inhibitory potential of the species were quantified by determining the half-maximal inhibitory concentration (IC_{50}) for each inhibitor. On the basis of the IC_{50} values, the inhibitors could be arranged in the following order of potency, $DPV > PV_2 > PV_3 > PV_4 > PV_1$ and in case of pMo compounds the following trend has been observed: $DMo_1 > PMo_2 > DMo_2 > PMo_3 > PMo_1$.⁶² In order to identify the mode of inhibition of the model enzyme by the inhibitor species, detailed kinetic investigations were carried out. The kinetic parameters, V_{max} (the maximum velocity) and K_m (Michaelis constant) were evaluated by using Lineweaver-Burk (LB) double reciprocal plots. Straight lines were obtained from the kinetic measurements at different substrate concentrations in presence of each of the inhibitors with a point of intersection in the second quadrant. As demonstrated by the LB plots (figure 6) an increase in concentration of each of the polymeric

Figure 4. ^{51}V NMR spectra of 0.2 mM aqueous solution of (a) PV_1 and (b) PV_4 .⁶² Reprinted with permission from ref. ⁶² Copyright (2011) American Chemical Society.

complexes led to a considerable decrease in $V_{\max}$ although K_m remained unaffected suggesting a non-competitive type of inhibition by these complexes. In contrast, the LB plots obtained when DPV or any of the free pMo complexes was used as inhibitor, were typical of mixed-type of inhibition of the enzyme combining competitive and non-competitive modes of inhibition. The values of K_i and K_{ii} , inhibitor constants for the competitive and non-competitive inhibition, respectively were evaluated (figure 6) in order to measure the affinity of the enzyme for the inhibitor, are presented in table 1.

For each of the macromolecular complexes value of K_i was found to be equal to K_{ii} , which is characteristic of a non-competitive inhibitor. For free diperoxovanadate as well as pMo complexes, $K_{ii} > K_i$ as is the case with a mixed type of inhibitor with major mode of inhibition being of the competitive type. Thus the two classes of complexes examined, anchored and free monomeric or dinuclear peroxometallates, exhibit distinct mechanistic preferences for phosphatase inhibitory activity. The neat complexes induced mixed type of inhibition of the function of the model enzymes, whereas the macrocomplexes served as classical non-competitive inhibitors.

Owing to large size of the macromolecular complexes they are unlikely to be capable of approaching the

Figure 5. Effect of compounds PV_1 , PV_2 , PV_3 , PV_4 , DPV , PMo_1 , PMo_2 , PMo_3 , DMo_1 , DMo_2 and free polymers (P) on activity of ALP from rabbit intestine. The ALP catalyzed rates of hydrolysis of p-NPP at pH 10.0 were determined at 30°C by measuring A_{405} in a reaction mixture containing ALP (3.3 $\mu\text{g}/\text{ml}$), p-NPP (2 mM) in incubation buffer (25 mM glycine + 2 mM MgCl_2 , pH 10.0) in the absence or presence of stated concentrations of the inhibitors. Effects of the additions are represented as the percent values (rounded to integers) of control ($\Delta\text{p-NPP} = 3.13 \mu\text{M}/\text{min}$). The data are presented as the means $\pm$ SE from three separate experiments. For polymeric compounds concentrations are on the basis of peroxometal loading.⁶² Reprinted with permission from ref. ⁶² Copyright (2011) American Chemical Society.

enzyme active site and hence would possibly prefer to interact with the enzyme at a site away from the active site which may result in change in overall conformation of the protein and inhibition of its function in a non-competitive manner.¹⁰⁶ Even the non-competitive inhibition induced by molybdate and tungstate on bovine spleen purple acid phosphatase was previously ascribed to the larger size of these ions.¹⁰⁶ The importance of redox properties of peroxo compounds has also been documented in inhibition of protein phosphatases.³⁸ It was reported earlier that peroxovanadate effectively inhibited the tyrosine phosphatase by oxidizing the critical cysteine residue in catalytic domain of the enzyme.^{30,38} It is known that the presence of such groups in and around the active centre of the enzymes are essential for the activity and in stabilization of the quaternary structure of the enzyme.¹⁰⁷ Taking into account these observations and our own findings on the oxidant activity of the complexes under investigation,⁶¹ it may be logical to expect that the compounds exert their inhibitory effect by interacting with the essential groups susceptible to oxidation such as $-\text{SH}$.^{39,108} For the free pV or pMo compounds, being smaller in size, both the mechanisms i.e., transition state analogy as well as oxidation ability of these compounds are

Figure 6. Lineweaver-Burk plots for inhibition of ALP activity in absence and presence of (A) PV_3 , (B) PMO_2 , (C) DPV and (D) DMO_1 . The inset represent secondary plot of initial kinetic data of Lineweaver plot. The reaction mixture contained glycine buffer (25 mM glycine + 2 mM $MgCl_2$, pH 10.0) and p-NPP (2–5 mM). The reaction was started by adding ALP (3.3 $\mu g/ml$) to the reaction solution which was pre-incubated for 5 mins and the rate of hydrolysis in the presence of $\blacklozenge$ 0 μM ; $\blacksquare$ 5 μM ; $\blacktriangle$ 10 μM ; $\times$ 15 μM ; $\bullet$ 20 μM ; $\bullet$ 25 μM inhibitors were obtained. The values are expressed as means $\pm$ SE from three separate experiments. Inset: (a) The Slopes were plotted against inhibitor concentrations and K_i values were obtained from the x-intercepts of these replots. (b) The vertical intercepts were plotted against inhibitor concentration and K_{ii} values were obtained from the x-intercepts of these replots. For polymeric compounds concentrations are on the basis of peroxometal loading.⁶² Reprinted with permission from ref.⁶². Copyright (2011) American Chemical Society.

likely to be responsible for the mixed inhibition displayed by these compounds combining competitive and non-competitive pathways.⁶² However, being aware of the complex nature of the species involved and their reaction with the biomolecules, and in absence of direct evidence, we are constrained in commenting on the actual pathway of inhibition of the model enzymes by the tested compounds.

4.3 WSP anchored peroxovanadium complexes as bromide oxidants

The contemporary interest in the bromination of organic substrates, particularly aromatics, has to a great extent been fuelled by the utility of bromo-organics as important precursors to numerous industrially valuable products ranging from pharmaceutically important

Table 1. Half-maximal Inhibitory Concentration (IC_{50}), and Inhibitor Constants (K_i and K_{ii}) Values for pV and pMo Compounds and Other Inhibitors Against ALP⁶² [reprinted with permission from ref.⁶². Copyright (2011) American Chemical Society].

Inhibitor	IC_{50} (μ M)	K_i (μ M)	K_{ii} (μ M)	K_{ii}/K_i	Type of inhibition
PV₁	72.45	71.42	70.38	0.99	Non-competitive
PV₂	41.34	49.29	48.50	0.98	Non-competitive
PV₃	45.25	54.50	53.80	0.98	Non-competitive
PV₄	52.54	59.98	59.71	0.99	Non-competitive
PMo₁	48.64	31.72	30.31	0.95	Non-competitive
PMo₂	16.92	17.10	16.80	0.98	Non-competitive
PMo₃	18.27	19.20	18.90	0.98	Non-competitive
DPV	25.18	9.13	21.22	2.30	Mixed Inhibition
DMo₁	16.90	6.00	21.50	3.58	Mixed Inhibition
DMo₂	17.94	7.50	24.50	3.27	Mixed Inhibition
Free polymer	—	—	—	—	—

Note: The ALP catalyzed rates of hydrolysis of p-NPP at pH 10.0 were determined at 30°C by measuring A_{405} in a reaction mixture containing ALP (3.3 μ g/ml), p-NPP (2 mM) in incubation buffer (25 mM glycine + 2 mM $MgCl_2$, pH 10.0) in the presence of stated concentrations of the inhibitors. The V_{max} and K_m in absence of inhibitor were found to be 7.9 μ M/min and 2.85 mM respectively. For polymeric compounds concentrations are on the basis of peroxometal loading.

compounds to pesticides and fire retardants.^{109,110} Vanadium Bromoperoxidases (V-BPO), present in several marine organisms, catalyze bromination by using H_2O_2 and bromide salts instead of Br_2 ,^{111,112} leading to the biosynthesis of a variety of naturally occurring brominated products. The enzymes catalyze bromide oxidation to generate an oxidized bromine species, likely to be equivalent of $BrOH$, Br_2 , Br_3^- or an enzyme-bound bromonium ion-type species, capable of transferring bromine atoms to acceptor molecules with electron rich π bonds.¹¹³ The mode of action of these enzymes spurred the development of plethora of functional V-BPO mimics based mainly on d^0 complexes such as vanadium,^{40,114–120} molybdenum^{30,31,119,121,122} and tungsten.^{29,30,123,124} However, in contrast to natural V-BPO which is most efficient at pH 5.5–7, most of the model complexes reported, were found to be catalytically active only in presence of acid.^{1,6,32,113,125}

Our group has a long standing interest in developing functional mimics of haloperoxidases with an ability to mediate organic oxidations under mild condition.^{100–102,126–130} A number of monomeric and dimeric peroxotungsten (pW) complexes,^{101,102,126} and a series of dinuclear pV compounds with the distinctive feature of having a μ -peroxo group of the type $[V_2O_2(O_2)_3(L)_3] \cdot H_2O$ ($L = asn, gln, gly-gly, gly-ala$ or $gly-asn$)^{127–129} could instantaneously oxidize bromide to a bromination competent intermediate in phosphate buffer, at near neutral pH. These compounds also efficiently mediated bromination of a variety of organic substrates in aqueous-organic media. The μ -peroxo vanadium compounds however, rapidly degrade in solution with loss of its high bromination activity. Nevertheless, we could foresee potential of such compounds

in biomimetic oxidative bromination provided it could be obtained in a stable form. Having gained an access to the set of stable and water soluble pV macrocomplexes, we decided to examine their activity in bromide oxidation in aqueous medium. The water based reactions are gaining importance in different catalytic reactions⁶⁴ in view of the growing environmental concerns in recent years.

We have used the method of de Boer *et al.*¹³¹ of introducing four bromine atoms into the molecule of phenol red ($\epsilon^{433} \text{ mM} = 19.7$) to form a bromophenol blue ($\epsilon^{592} \text{ mM} = 67.4$) to assess the bromination activity of the compounds in water. Phenol red undergoes facile stoichiometric bromination to form its tetra brominated product bromophenol blue, which can be monitored spectrophotometrically (figure 7). The yellow colour of the standard reaction solution containing phenol red and bromide in phosphate buffer gradually changed to blue on addition of the freshly prepared aqueous solution of each of the compounds, **PV₁–PV₄** at concentrations indicated in table 2. The spectrum recorded showed a decrease in absorbance of the peak at A_{433} and a new peak at A_{592} characteristic of the product bromophenol blue (figure 7). From the results summarized in table 2, it is evident that **PV₁** and **PV₄** with dimeric diperoxovanadate units possess bromination activity. The bromination activity could be restored by the addition of H_2O_2 to the spent reaction mixture which contained excess bromide and substrate. The active brominating species thus afforded regeneration *in situ* in presence of exogenous H_2O_2 , which could be recycled for further conversion without change in its activity. It was intriguing to note that under the optimized conditions, the neat DPV complex was totally inactive in bromination and

Figure 7. Bromination activity with **PV₁**. (a) The increase of A_{592} for bromophenol blue indicating the rate of bromination of phenol red with **PV₁**. The reaction mixture contained phosphate buffer (0.05 M, pH 5.5), KBr (1 M) and phenol red (20 μ M) and **PV₁** (0.11 mg/ml). (b) Spectral changes at 2 min interval following bromination of phenol red to bromophenol blue on addition of compound solution to the reaction mixture are shown in the inset.⁶¹ Reprinted from ref. ⁶¹, Copyright (2008), with permission from Elsevier.

PV₂ and **PV₃** with monomeric pV units showed poor oxidant activity affording the brominated products in <5% yield.⁶¹ The findings are consistent with the previous suggestion implicating formation of a peroxo-bridged divanadate intermediate as active brominating species at neutral pH.^{5,127,128}

Scope of using the pV complexes for mediating bromination of various other organic substrates has also been explored in aqueous-organic media.⁶¹ Smooth conversion of several activated aromatics into their corresponding bromo-organics were achieved by stirring a solution of the substrate in presence of **PV₁** or **PV₄** in $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (1:1) for 7–10 h at ambient temperature. A 1:1 oxidant:substrate stoichiometry appeared to be optimal for the reaction. Results obtained by using **PV₁** as a representative are presented in table 3.

Activated aromatics such as aniline and acetanilide were brominated to produce predominantly p-bromo products. Preferential bromination at either ortho or para position of the aromatic ring leading to mono substitution indicated an electrophilic bromination mechanism. The oxidant **PV₁** or **PV₄** could be regenerated easily by treating the aqueous extract of the spent reaction mixture with H_2O_2 , followed by the addition of DMF to induce precipitation of the compounds. Reuse of the recovered complex in a fresh cycle of bromination reaction afforded the desired brominated products indicating that metal complexes remain intact with the polymer chain. However, a slight decrease in

product yield obtained suggested the possibility of some leaching of the metal over subsequent reuse of the compound. The remarkable feature of the present methodology is that the reaction takes place at near neutral pH and no extra addition of acid or H_2O_2 is required for the stoichiometric bromination reaction of the substrate.

5. Polymer immobilized pMo compounds

5.1 Synthesis and characterization

Immobilization of active soluble catalysts on insoluble polymeric resin usually leads to heterogenization of homogeneous catalysts, offering an effective solution to separation and recovery of the catalyst. Our interest in attaching pMo species to insoluble polymer resin to obtain macrocomplexes has been stimulated mainly by the prospect of generating newer potential heterogeneous catalysts for organic oxidations. We have selected two types of polymer matrices for immobilization of pMo species, viz., amino acid functionalized Merrifield resin (**MR**)⁶⁶ and poly(acrylonitrile) (**PAN**).⁶⁵ **PAN** was chosen due to its being an insoluble, non-toxic, cost-effective and commercially available reagent.¹³² As far as we are aware, the pW immobilized compound **PANW** reported previously by us,⁶⁴ is the only example where **PAN** has been used as support for immobilization of peroxometal compound⁴⁴ despite the well-documented application of acrylonitrile polymers in many areas ranging from medicine to textiles treatment.¹³² On the other hand, divinyl benzene cross-linked polystyrene or the Merrifield resin (**MR**) still remains the most popular solid support mainly owing to its ability to undergo facile functionalization,^{46,47} ready availability, low cost and chemical stability.^{119,133,134} Over the past decades, a multitude of transition metal catalysts supported on **MR**, for various organic transformations were reported which have been reviewed recently.^{135–137} Functionalization of the resin with appropriate ligand groups is the most important step towards establishing stable metal-polymer linkage^{51,64,138} which can resist the metal species from leaching out of the polymer matrix as a result of repeated catalytic cycles. The first synthesis of metal complexes supported on cross-linked poly(styrene–divinylbenzene) resin through amino acid group involving copper(II) ion was reported in the year 1977.¹³⁹ Subsequently, application of ruthenium(III) and palladium(II) complexes supported to L-valine functionalized **MR** as catalysts in olefin oxidation and hydrogenation, respectively, were reported by Valodkar *et al.*^{140,141}

Table 2. Bromination of phenol red with peroxovanadate complexes **PV**₁–**PV**₄.⁶¹

No.	Compounds	Conc. (mM) in terms of pV loading	Rate of bromine transfer	
			$\Delta A_{592}/\text{min}$	$\mu\text{M Br}/\text{min}$
1.	[V ₂ O ₂ (O ₂) ₄ (carboxylate)]-PA(PV ₁)	0.2	0.052	3.1
2.	[V ₂ O ₂ (O ₂) ₄ (carboxylate)VO(O ₂) ₂ (sulfonate)]-P(SS-co-M) (PV ₄)	0.2	0.045	2.7
3.	[VO(O ₂) ₂ (carboxylate)]-PMA(PV ₂)	0.2	–	–
4.	[VO(O ₂) ₂ (sulfonate)]-PSS(PV ₃)	0.2	–	–

Reaction conditions: phosphate buffer (50 mM, pH 5.5), KBr (1 M), phenol red (20 μM) and compound (0.2 mM pV).

No report however, seems to exist on anchoring of pMo species to amino acid functionalized Merrifield resin.

The compounds, [MoO₂(O₂)(L)₂]²⁻–MR [L = valine (**MRV****Mo**) or alanine (**MRAM****Mo**) and **MR** = Merrifield resin] have been synthesized by adopting a two-step methodology. The functionalized polymer, **MRV** and **MRA** was obtained by reacting the polymer with the respective amino acid in methanol and using pyridine as a base, according to a previously established procedure.¹⁴¹ The reaction of **MRV** or **MRA** with H₂MoO₄ in presence of 30% H₂O₂ afforded the

compounds **MRV****Mo** and **MRAM****Mo**.⁶⁶ The synthesis of the poly(acrylonitrile) anchored compound, **PAN****Mo** was achieved by allowing the polymer to swell in a reaction mixture consisting of peroxomolybdenum species, generated *in situ* by reacting H₂MoO₄ with 30% H₂O₂.⁶⁵

The compounds were characterized by elemental analysis, spectral studies (FTIR, ¹³C NMR and ⁹⁵Mo NMR and diffuse reflectance UV-Vis), SEM, EDX, Brunauer–Emmett–Teller (BET) and TGA-DTG analysis.⁶⁶ About 70% of the ligand units have been estimated

Table 3. Bromination of organic substrates mediated by compound **PV**₁⁶¹ [reprinted from ref. ⁶¹, Copyright (2008), with permission from Elsevier].

Substrate	Product	% Yield	Time (h)
Salicylaldehyde		80	10
Acetanilide		82	10
Anisidine		75	8
<i>o</i> -Aminophenol		83	8
<i>p</i> -Aminophenol		85	8
<i>m</i> -Aminophenol		a: 77, b: 18	8
Aniline		a: 80, b: 15	8
<i>o</i> -Nitroaniline		a: 70, b: 23	7
<i>m</i> -Nitroaniline		a: 65, b: 30	7
<i>p</i> -Nitroaniline		a: 75, b: 21	7
<i>o</i> -Methoxytoluene		a: 60, b: 25	8

Reaction conditions: substrate (0.5 mmol), Et₄NBr (2.0 mmol), and **PV**₁ (0.25 g, 0.5 mmol V) in CH₃CN/H₂O (1:1, 5 mL) at room temperature.

Figure 8. XPS spectra of Mo ($3d_{3/2}$) and Mo ($3d_{5/2}$) peaks for (a) **MRVMo** and (b) **MRAMo**.⁶⁶ Reproduced from Ref. ⁶⁶ with permission from The Royal Society of Chemistry.

to be bound to pMo moieties in **MRV** (60% in **MRA**). Figure 8 represents the Mo ($3d$) XPS spectra of the polymer anchored pMo complexes, **MRVMo** and **MRAMo**. The catalysts displayed characteristic $3d_{5/2}$ and $3d_{3/2}$ doublets with peaks located at 232.7 and 235.9 eV, respectively and binding energy values for Mo ion in oxidation state of 6+.^{142,143} The single resonance in ^{95}Mo NMR spectra occurred at -116 ppm and -115 ppm (relative to $[\text{MoO}_4]^{2-}$) for **MRVMo** and **MRAMo**, respectively (figure 9) which is in the region characteristic of monoperoxomolybdate species.⁹¹

A structural feature common to each of the immobilized compound was observed to be the presence of pMo species in its dioxomonoperoxo form. In the compounds, **MRVMo** and **MRAMo**, the pMo moieties are unidentately co-ordinated via O (carboxylate) atoms of the pendant amino acid ligands (figure 10a, b).⁶⁶ In case of the compound **PANMo**, the pMo moieties are anchored to the polymeric chain through N atom of nitrile groups (figure 10c).⁶⁵

5.2 Catalytic activity in sulfide oxidation

Importance of sulfoxides and sulfones as commodity chemicals, their utility as versatile building blocks for construction of chemically and biologically useful molecules including therapeutic agents, are well-documented in the literature.^{144–148} Research efforts towards developing viable and environmentally benign synthetic

Figure 9. ^{95}Mo NMR spectra of (a) **MRVMo** and (b) **MRAMo** in $(\text{CCl}_4/\text{DMSO-d})$ (80:20, v/v).⁶⁶ Reproduced from Ref. ⁶⁶ with permission from The Royal Society of Chemistry.

methodologies for oxidation of organic sulfides to sulfoxides and sulfones appear to have intensified, in recent times.^{149–151} We could achieve clean conversion to high purity sulfoxide or sulfone from the corresponding sulfides as well as dibenzothiophene (DBT), in presence of catalytic amounts of the compounds **MRVMo** or **MRAMo** in impressive yields and TOF, by establishing appropriate reaction conditions.

From the results presented in table 4, it is evident that the reaction conducted at the molar ratio of substrate: H_2O_2 at 1:2 and Mo:substrate at 1:1000 in methanol proceed smoothly at room temperature, to yield the respective sulfoxide as the exclusive product. Significantly, even after a prolonged reaction time, no overoxidation to sulfone was noted. A blank reaction conducted without the catalyst was observed to be slow and non-selective affording a mixture of sulfoxide and sulfone in very low yield.⁶⁶

We have further compared the heterogeneous phase reaction with the homogeneous one by conducting the oxidation reaction in presence of soluble unsupported peroxomolybdenum species in lieu of the heterogeneous catalyst **MRAMo** or **MRVMo**, under otherwise identical reaction conditions. It was found that oxidation of MPS although could be achieved in presence of neat pMo catalyst, the reaction was non-selective leading to a mixture of sulfoxide and sulfone, with a TOF nearly 5-fold lower compared to that obtained in presence of the heterogeneous analogue.⁶⁶

Importantly, in presence of the newly developed catalysts, a much less nucleophilic refractory sulfide, such as DBT (table 4, entry 12) afforded selective oxidation to sulfoxide. Aliphatic sulfides were more readily oxidized than the aromatic sulfides and dialkyl sulfides were oxidized at faster rate relative to allylic and vinylic sulfides (table 4, entries 8 and 9). This trend may be expected since it has been known that rate of oxidation

Figure 10. Proposed structure of polymer anchored compounds, (a) **MRAMo**, (b) **MRVMo** and (c) **PANMo**. “~~~~” represents polymer chain.^{65,66} Reprinted from ref.⁶⁵, Copyright (2013), with permission from Elsevier, reproduced from Ref.⁶⁶ with permission from The Royal Society of Chemistry.

Table 4. Selective oxidation of sulfides to sulfoxides with 30% H_2O_2 catalyzed by **MRAMo** and **MRVMo**^a at room temperature or 65°C^b (values within parenthesis)⁶⁶ [reproduced from Ref.⁶⁶ with permission from The Royal Society of Chemistry].

$\text{R}^1-\text{S}-\text{R}^2 \xrightarrow[\text{Methanol}]{\text{MRAMo or MRVMo (Mo:S=1:1000), 30\% H}_2\text{O}_2 \text{ (2 equivalent)}} \text{R}^1-\text{S}(=\text{O})-\text{R}^2$									
		MRAMo				MRVMo			
Entry	Substrate	Time (min)	Isolated Yield (%)	TON ^c	TOF ^d (h ⁻¹)	Time (min)	Isolated Yield (%)	TON ^c	TOF ^d (h ⁻¹)
1	PhSCH ₃	40 (15)	98 (99)	980 (990)	1470 (3960)	45 (17)	97 (99)	970 (990)	1293 (3494)
		40 (15)	96 (97) ^e	960 (970)	1440 (3880)	45 (17)	95 (97) ^e	950 (970)	1266 (3423)
		40 (15)	98 (97) ^f	980 (970)	1470 (3920)	45 (17)	97 (98) ^f	970 (980)	1293 (3458)
2	CH ₃ SCCH ₃	35	98	980	1680	40	97	970	1455
3	C ₄ H ₉ SC ₄ H ₉	40 (15)	98 (97)	980 (970)	1485 (3880)	45 (17)	96 (99)	960 (990)	1280 (3494)
4	C ₄ H ₉ SC ₃ H ₇	40 (15)	96 (99)	960 (990)	1455 (3960)	45 (15)	97 (98)	970 (980)	1293 (3920)
5	C ₆ H ₁₃ SC ₆ H ₁₃	40 (15)	97 (98)	970 (980)	1455 (3920)	45 (17)	98 (97)	980 (970)	1306 (3423)
6	PhSC ₂ H ₅	50 (20)	98 (96)	980 (960)	1176 (2880)	55 (20)	99 (98)	990 (980)	1080 (2940)
7	PhSC ₂ H ₄ -OH	100 (30)	96 (95)	960 (950)	576 (1900)	110 (40)	96 (98)	960 (980)	523 (1470)
8	PhSCH ₂ -CH=CH ₂	80 (20)	98 (96)	980 (960)	735 (2880)	90 (25)	97 (95)	970 (950)	646 (2280)
9	PhSCH=CH ₂	210 (80)	97 (95)	970 (950)	277 (712)	240 (85)	96 (98)	960 (980)	240 (691)
10	PhSPh	240 (90)	97 (96)	970 (960)	242 (640)	250 (95)	98 (97)	980 (970)	235 (612)
11	PhSCH ₂ -Ph	90 (30)	98 (95)	980 (950)	653 (1900)	110 (35)	96 (98)	960 (980)	523 (1680)
12 ^g	Dibenzothiophene	(10 h)	(96)	(96)	(9.6)	(10 h)	(94)	(94)	(9.4)

^a All reactions were carried out with 5 mmol substrate, 10 mmol 30% H_2O_2 and catalyst (0.005 mmol of Mo) in 5 mL methanol at RT, unless otherwise indicated. ^b Reaction at 65°C in refluxing methanol. ^c TON (Turnover number) = mmol of product per mmol of catalyst. ^d TOF (Turnover frequency) = mmol of product per mmol of catalyst per hour. ^e Yield of 6th reaction cycle. ^f Yield at 7.5 g scale. ^g Substrate (5 mmol), catalyst (0.05 mmol of Mo), methanol (5 mL).

of sulfides by H_2O_2 increases with the increased nucleophilicity of the sulfide.^{152,153} The catalyst exhibited excellent chemoselectivity toward sulfur group of substituted sulfides with co-existing oxidation prone functional groups such as allylic, vinylic, benzylic or alcoholic groups (table 4, entries 7, 8, 9 and 11). Owing to their heterogeneous nature, the catalysts could be easily separated from the spent reaction mixture by filtration, and recycled for at least up to six reaction cycles without loss of their catalytic activity or product selectivity. The reaction could also be conveniently conducted on a larger scale as shown in the table 4 (entry 1^f). These important features demonstrate the synthetic value of the protocol.

Significantly, we have also achieved the chemoselective oxidation of sulfides to pure sulfone by using 4 equivalents of 50% H_2O_2 , and using acetonitrile as solvent in lieu of MeOH in presence of the same pMo catalysts (scheme 1). A proposed mechanistic scheme which satisfactorily explains the experimental findings, is shown in figure 11.⁶⁶ The mechanism is in accord with previous observations that, formation of an oxo-diperoxo configuration [reaction a] may be essential^{31,126,154} for a pMo species to be catalytically active in oxidation.

5.3 Catalytic activity in oxidative bromination

Activity of the immobilized complex **PANMo**, as well as its tungsten containing analogue, **PANW** as heterogeneous catalysts in oxidative bromination of a series of structurally diverse aromatic compounds have been investigated.⁶⁵ The data presented in table 5 show that the compound, **PANMo** catalyzed the reaction of the substrate with bromide, in presence of the terminal oxidant H_2O_2 and Mo:substrate and Br^- : oxidant molar ratio maintained at 1:10 and 1:4, respectively in $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (1:1) to afford the corresponding brominated products in impressive yield.⁶⁵

The notable feature of the synthetic procedure is that the reaction takes place under mild condition at room temperature, at near neutral pH or the natural pH of the reaction mixture, and no extra addition of acid or alkali

Figure 11. Proposed catalytic cycle for sulfide oxidation with **MRaMo** as representative.⁶⁶ Reproduced from Ref. ⁶⁶ with permission from The Royal Society of Chemistry.

is required for the bromination reaction. It is notable that a significant increase in TOF of the reaction was observed when conducted in presence of perchloric acid at a highly acidic pH, nevertheless, addition of acid or halogenated solvents were strategically avoided as far as possible, in order to maintain an environmentally clean reaction condition. The catalyst could be recovered and recycled without further conditioning, after separating it from the spent reaction mixture after completion of each cycle of bromination, by charging it with H_2O_2 , a fresh lot of substrate and bromide.⁶⁵

Based on our findings a scheme of reactions shown in figure 12 has been proposed.⁶⁵ The first step is likely to be the formation of the reactive diperoxomolybdate species **II** from the monoperoxomolybdate species **I**, in

Scheme 1. Optimized reaction conditions for the selective oxidation of sulfides to sulfoxides or sulfones by pMo compounds.⁶⁶ Reproduced from ref. ⁶⁶ with permission from The Royal Society of Chemistry.

Table 5. Bromination of organic substrates with 30% H₂O₂ catalyzed by **PANMo**^{a65} [reprinted from ref. ⁶⁵, Copyright (2013), with permission from Elsevier].

Entry	Substrate	Product	Time (h)	Yield	TOF ^b (%) (h ⁻¹)
1	Aniline	4-Bromoaniline 2-Bromoaniline	0.41	83 14	23.27
2	p-aminophenol	4-Amino-3-bromophenol	0.75	95	12.66
3	m-aminophenol	5-Amino-2-bromophenol 3-Amino-4-bromophenol	0.66	75 20	14.39
4	o-aminophenol	2-Amino-5-bromophenol	0.75	97	12.93
5	p-nitroaniline	2-Bromo-4-nitroaniline 2,6-Dibromo-4-nitroaniline	1.00	84 13	9.70
6	m-nitroaniline	2-Bromo-5-nitroaniline 4-Bromo-3-nitroaniline	0.83	83 15	11.80
7	o-nitroaniline	4-Bromo-2-nitroaniline 2-Bromo-6-nitroaniline	1.00	85 11	9.60
8	Quinol	2-Bromobenzene-1,4-diol	2.00	97	4.85
9	Pyrogallol	4-Bromobenzene-1,2,3-triol	1.33	97	7.29
			1.33	96 ^c	7.21
10	Resorcinol	4-Bromobenzene-1,3-diol	3.50	95	2.71
			3.50	94 ^c	2.68
11	Acetanilide	N-(4-bromophenyl)acetamide	1.50	97	6.46
12	Salicylaldehyde	5-Bromo-2-hydroxybenzaldehyde	2.50	97	3.88
			2.50	95 ^c	3.80
13	o-methoxytoluene	1-Methoxy-2-methyl-4-bromobenzene	1.16	95	8.18
14	Catechol	4-Bromo-1,2-dihydroxybenzene	2.00	94	4.70

^aReaction conditions: substrate(1.0 mmol), KBr(4.0 mmol), 30% H₂O₂ (16.0 mmol) and **PANMo** (0.129 g, 0.1 mmol Mo) in CH₃CN/H₂O (1:1, 5 mL) at RT.

^bTOF (Turnover frequency) = mmol of product per mmol of metal per hour.

^cYield of 6th reaction cycle.

presence of H₂O₂ (reaction a), as has been proposed in case of **MRAMo** catalyzed sulfide oxidation.

It is noteworthy that monoperoxo species of Mo, which is known to be inactive in organic oxidations,

could serve as efficient heterogeneous catalysts for H₂O₂ induced sulfide oxidation as well as oxidative bromination, apparently as a consequence of its immobilization.

Figure 12. The proposed mechanism of **PANMo** catalyzed oxidative bromination in presence of H₂O₂.⁶⁵ Reprinted from ref. ⁶⁵, Copyright (2013), with permission from Elsevier.

6. Conclusion

In this brief account of our work we intended to demonstrate that it is possible to gain access to stable and structurally defined metal containing macromolecules by anchoring the peroxometal species to appropriate polymer matrices. It is remarkable that the compounds retain their structural integrity in solution not only at higher pH but also under acidic conditions. The compounds thus show prospect of being useful for *in-vivo* study even at strongly acidic condition. Additional important biorelevant characteristic of these complexes include their distinct mechanistic preference to inhibit function of phosphohydrolases non-competitively, in contrast to the mixed type of inhibition displayed by the free peroxo complexes. These macrocomplexes may therefore be expected to serve as selective probes for non-competitive site of inhibition of phosphohydrolases. Some of the WSP anchored pV compounds stoichiometrically oxidized bromide to a bromination competent intermediate in aqueous medium at physiological pH, an essential requirement of a biomimetic model. Significantly, neither additional H_2O_2 nor acid is required for the bromination activity of the pV complexes. In our previous work,⁶¹ it has been shown that the macrocomplexes exhibited enhanced resistance to degradation under the effect of the powerful enzyme catalase. Moreover, *in-vivo* studies revealed that polyacrylate bound pV (PV_1) exerted vasomodulatory effect on rat aortic rings.¹⁵⁵ It is hoped that the information obtained from the present study will help in identifying the right macroligand environment for peroxo metal derivatives to carry forward for *in vivo* studies. These interesting findings clearly show that a lot remains to be unravelled on other possible chemical and biochemical applications of this class of new materials.

Immobilization of pMo on insoluble polymer resin such as DVB cross-linked MR and PAN, afforded a set of supported monoperoxo complexes. These compounds could be successfully used as heterogeneous catalysts for selective oxidation of sulfides to obtain sulfoxide or sulfone from the corresponding aryl or alkyl sulfide and DBT, employing H_2O_2 , in excellent yield and high TOF by a versatile variation of reaction conditions. The catalysts provide complete control over degree of oxidation of the product. The same catalysts were also efficient in catalyzing H_2O_2 induced oxidative bromination of a variety of aromatic substrates to afford bromo organics in impressive yields under mild reaction conditions, similar to the bromoperoxidase catalyzed reactions. The developed procedures are free from halogenated solvent or any other additives such as acid or a co-catalyst, and hence are environmentally

clean and safe. Their easy regeneration and reusability for several catalytic cycles without any change in activity are additional attractive attributes of the catalysts. The catalytic protocols thus adhere to several guiding principles of 'green' chemistry.

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