CHAPTER IV

DIMERIC CARBOXYLATE COMPLEXES OF COPPER(II) AS HOMOGENEOUS CATALYSTS IN AEROBIC OXIDATION OF BENZYL ALCOHOL
ABSTRACT

Catalytic properties of a few dinuclear copper(II) complexes viz. \([\text{Cu}_2(\mu-O_2\text{C}_7\text{H}_{15})_4(4-\text{CNpy})_2] \) (Ib), \([\text{Cu}_2(\mu-O_2\text{C}_7\text{H}_{15})_4(3-\text{CNpy})_2] \) (IIb) and \([\text{Cu}_2(\mu-O_2\text{C}_7\text{H}_{15})_4(4-\text{Mepy})_2] \) (IIIb) are described and results are compared with results obtained using a few related species viz. \([\text{Cu}_2(\mu-O_2\text{C}_6\text{H}_5)_4(4-\text{Mepy})_2] \) (IV), \([\text{Cu}_2(\mu-O_2\text{C}_6\text{H}_5)_4(4-\text{Etpy})_2] \) (V), \([\text{Cu}_2(\mu-O_2\text{CCH}_3)_4(4-\text{Mepy})_2] \) (VI) and \([\text{Cu}_2(\mu-O_2\text{C}_6\text{H}_5)_4(4-\text{DMAP})_2] \) (VII) (CNpy= cyanopyridine, Mepy= methylpyridine, Etpy= ethylpyridine, DMAP= N,N-dimethylaminopyridine) in the selective oxidative transformation of benzyl alcohol. The reactions are carried out under homogeneous aerobic conditions in presence of TEMPO (2,2′,6,6′-tetramethylpiperidine-oxyl) as co-catalyst. A catalytic amount of copper(II) complex (1 mol%) and TEMPO (5 mol%) in acetonitrile medium allow the selective oxidation of benzyl alcohol to only benzaldehyde and no benzoic acid. Out of all the complexes, \([\text{Cu}_2(\mu-O_2\text{C}_7\text{H}_{15})_4(4-\text{Mepy})_2] \) (IIIb) gives the best results with 100% conversion of benzyl alcohol to benzaldehyde in 12 hours.
4.1 INTRODUCTION

Conversion of alcohols to aldehydes and ketones is one of the most important and widely used oxidation reactions in organic chemistry.\(^1\,^2\) Traditional methods to carry out these type of conversions involve the use of stoichiometric amounts of inorganic oxidants such as pyridinium chlorochromate, pyridinium dichromate, \(\text{CrO}_3/\text{H}_2\text{SO}_4\) (Jones reagent), \(\text{KMnO}_4\), \(\text{MnO}_2\) etc.\(^3\) Although these reagents have widespread use in organic synthesis, the disadvantage is that they are toxic, expensive, difficult to dispose of, hazardous and non-catalytic. Therefore, such oxidants are rarely used in large scale industrial synthesis of organic chemicals. With the declining use of heavy metal oxidants, efforts have been made to develop more environmentally benign methods for alcohol oxidation. Selective and environment friendly oxidations catalyzed by transition metal complexes constitute a very important area of current research. From the green chemistry point of view, the best choice for replacing the above hazardous oxidants is to employ molecular oxygen or air as oxidant in the transformation of alcohols to aldehydes and ketones because oxidation with dioxygen produces water as the only by-product. Since molecular oxygen is a triplet in its ground state and so inert towards substrate oxidation, catalysts are therefore required to use molecular oxygen as the oxidant. The implementation of a transition metal based catalyst in combination with oxygen provides a highly useful method to replace the traditional procedures (Scheme I).\(^4\)
Copper seems to be an appropriate metal for the catalytic oxidation of alcohols because it is present in nature as part of the active site in a variety of enzymes such as galactose oxidase that selectively catalyze this conversion. The structure of galactose oxidase shows (Scheme II) that the Cu(II) ion is coordinated with a tyrosinate anion, a (thioether-modified) tyrosyl radical and two histidine residues. The mechanism of (mainly primary alcohol) oxidation by galactose oxidase has been extensively studied. Initially, Cu(II) ion coordinates the alcohol and then the H atom is abstracted from the α-carbon atom of the O-coordinated alkoxide ligand by the coordinated tyrosyl radical. This is taken to be the rate determining step forming a bound ketyl radical anion and tyrosine. Finally aldehyde is formed by the intramolecular conversion of the ketyl radical ligand through one electron oxidation with the formation of Cu(I) species. Active Cu(II)-tyrosil the enzyme is again formed by the reoxidation of the Cu(I) species by dioxygen where H₂O₂ is formed as the byproduct. A large number of model compounds have been synthesized with structures similar to that of galactose oxidase with a view to measuring their catalytic properties for the aerobic oxidation of alcohols.
One of the catalytic systems currently considered to be a galactose oxidase mimic is the copper/nitroxy radical catalyzed oxidation of alcohols which was first introduced by Brackman and Gaasbeek in 1966.\textsuperscript{12} Later Sammelhack \textit{et al.} reported copper-(TEMPO = 2,2,6,6-tetramethylpiperidine-oxyl) to be an efficient catalytic system for alcohol oxidation.\textsuperscript{13} They introduced CuCl/TEMPO catalytic system in the aerobic oxidation of activated primary alcohols using dioxygen as a stoichiometric oxidant where they got a turnover frequency of up to 9.6 h\textsuperscript{-1} at room temperature. Later, a large number of Cu/TEMPO based catalysts have been reported to be highly efficient for the conversion of a broad range of alcohols to aldehydes and ketones.\textsuperscript{14-18} Nitroxy radicals are increasingly applied on both laboratory scale and industrial scale for alcohol oxidation.\textsuperscript{19,20} Markó and co-workers have taken active role in the later developments of this type of system. Initially they reported that a combination of CuCl (5 mol\%), phenantroline (5 mol\%) and di-tert-butylazodicarboxylate, DBAD (5 mol\%) in presence of bases like K\textsubscript{2}CO\textsubscript{3} and Bu\textsuperscript{1}OK allowed a oxidation of a variety of primary alcohols in toluene with air or oxygen as oxidant.\textsuperscript{21} Punniyamurthy \textit{et al.} utilised a Cu(II)-salen complex with TEMPO for aerobic
oxidation of alcohol. Sheldon and group reported in 2003 that [CuBr₂(2,2'-bipyridine)] can catalyze the selective and very mild aerobic oxidation of primary alcohols to aldehydes in presence of TEMPO and a base (tert-BuOK) as a co-catalyst in acetonitrile:water (2:1). The solubility of the copper catalyst can be increased in presence of 2,2'-bipyridine and so beneficial electronic effects can be caused by the pyridine rings. Since then, a large number of copper complexes with various nitrogen donor ligands in combination with TEMPO have been employed as catalysts for the selective aerobic oxidation of alcohols. Different mechanisms have been proposed for the Cu/TEMPO catalytic systems. Extensive kinetic and spectroscopic analysis, computational work have been conducted to explore the catalytic cycle involving Cu⁺/Cu⁰, organic ligands, nitroxyl radical, molecular oxygen and the alcohol substrate in the complex reaction system.

Hoover and Stahl demonstrated the impressive functional group tolerance and selectivity for primary alcohols. Many primary allylic, benzylic and aliphatic alcohols were oxidized to the corresponding aldehyde using 5 mol% copper and 5 mol% TEMPO with 10 mol% N-methylimidazole in presence of various functional groups like heterocycles, alkenes and unprotected secondary alcohols. Substrates with vicinal diols and other chelating groups in close proximity to the reactive alcohol undergo poor conversions. Substrate competition reactions show that CuBr₂ is more selective than copper(II) triflate, Cu(OTf)₂ because the latter promotes over oxidation.

Ragauskas and Gree have developed methods for utilizing the Cu/TEMPO oxidation in ionic liquids in which products are extracted using organic solvents while copper and TEMPO containing ionic liquid can be recycled many times without losing their
activity. To enhance the recyclability of the catalyst, Knochel and his group used a biphasic solvent system (chlorobenzene/perfluorooctyl bromide) and a pyridine ligand having fluorinated ponytails for a CuBr-Me₂S-TEMPO catalytic system. With this system, they could reuse and recover the fluorous layer containing the catalyst almost up to eight times with a very little loss of activity.\(^3\)

From the selectivity and functional group tolerance point of view, the Cu/TEMPO catalyzed aerobic oxidation of alcohols is utilized in a number of total syntheses. For example Essigmann selectively oxidized a benzylic alcohol in the presence of an aliphatic primary alcohol during the synthesis of a known side product of the 2+2 reaction of psoralen, the parent compound in a family of natural products known as furocoumarins.\(^3\)

Although Cu(II) complexes are widely used as catalyst for oxidation of alcohol as well as aromatic hydrocarbon by dimeric paddle wheel Cu(II) complexes of the type \([\text{Cu}_2(\mu-O_2\text{CR})_4(L)_2]^{32}\) is virtually unknown, such dimeric complexes having N-based ligands like pyridines as axial ligands stabilized by four bridging carboxylato ligands have a great role to play in alcohol oxidation as it is known that catalytic efficiency of copper chloride in this type of transformation is enhanced by various N-containing ligands.\(^3\) Reedijk et al. employed various Cu(II) dimeric paddle wheel carboxylates in the catalytic oxidation of carboxylic acids.\(^3\) Rodgers and his co-workers reported acetylation of methyl-4-hydroxy benzoates catalyzed by some Cu(II) carboxylates.\(^3\) Chemler and his group reported that copper(II) carboxylates promotes intramolecular diamination and carboamination of terminal alkenes.\(^3\) Fish et al. reported a copper(II) carboxylate dimer \([\text{Cu}(_{8\text{F}_{17}}\text{CH}_2)_2\text{CHCO}_2]_2\) as catalyst in alcohol oxidation.\(^3\) They make use of some
fluorocarbon soluble Cu(II) carboxylates with nonfluoroponytailed nitrogen ligands as precatalysts for the oxidation of 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde under fluorous biphasic conditions in combination with TEMPO/O₂ as oxidant. Our group is specifically interested in invading the wide area of research regarding application of dimeric paddle wheel Cu(II) complexes as catalysts in organic transformations. Recently, our group reported some dimeric Cu(II) tetracarboxylates as catalysts in the oxidation of benzyl alcohols in presence of aqueous tert-butyl hydroperoxide (TBHP) as the oxidant.³⁸

Efficacy of the Cu/TEMPO based catalytic system encouraged many researchers to develop new copper complexes to be utilized in the aerobic oxidation of alcohols in combination with TEMPO. Figiel et al. introduced a greener chemical transformation and reported that the selective aerobic oxidation of benzyl alcohol to the corresponding benzaldehyde could be accomplished using sole water as the solvent without using any organic or alternative solvent employing a multinuclear copper(II) compound in combination with TEMPO at 25-80°C.³⁹ Most of the literature reports that the bpy/TEMPO based catalysts were generally used as catalyst precursors for the copper catalyzed aerobic oxidation of alcohols in the presence of tert-BuOK as co-catalyst. The complexes were obtained in-situ from the ligands with CuBr₂ in a 2:1 acetonitrile/water mixture which selectively catalyzed the aerobic oxidation of primary benzylic, allylic and aliphatic alcohols and secondary benzylic alcohols.

We have synthesized a few long chain dimeric Cu(II) carboxylate complexes with pyridyl ligands as discussed in previous chapters. These long chain complexes remain unexplored regarding their use as homogeneous oxidation catalyst. It was an interesting task
to compare their catalytic properties with that of the known dimeric paddle wheel copper(II) complexes particularly because the presence of the long alkyl chains in the complexes is likely to improve the solubility of the complexes in organic media wherein the catalytic reactions are usually carried out. So, in this chapter we put forward a comparison of the catalytic properties of three newly synthesized long chain copper(II) complexes having substituted pyridyl ligands viz. \([\text{Cu}_2(\mu-O_2\text{CC}_7\text{H}_{15})_4(4-\text{CNpy})_2] (\text{Ib})\), \([\text{Cu}_2(\mu-O_2\text{CC}_7\text{H}_{15})_4(3-\text{CNpy})_2] (\text{IIb})\) and \([\text{Cu}_2(\mu-O_2\text{CC}_7\text{H}_{15})_4(4-\text{Mepy})_2] (\text{IIIb})\) with that of previously synthesized complexes in our lab viz. \([\text{Cu}_2(\mu-O_2\text{CC}_6\text{H}_5)_4(4-\text{Mepy})_2] (\text{IV})\), \([\text{Cu}_2(\mu-O_2\text{CC}_6\text{H}_5)_4(4-\text{Etpy})_2] (\text{V})\), \([\text{Cu}_2(\mu-O_2\text{CC}_6\text{H}_5)_4(4-\text{Mepy})_2] (\text{VI})\) and \([\text{Cu}_2(\mu-O_2\text{CC}_6\text{H}_5)_4(4-\text{DMAP})_2] (\text{VII})\) (CNpy=4-cyanopyridine, Mepy= methylpyridine, Etpy= ethylpyridine, DMAP= N,N-dimethylaminopyridine). All these complexes are employed in the aerobic oxidation of alcohols in presence of TEMPO as the co-catalyst.

4.2 EXPERIMENTAL

4.2.1 Instruments and chemicals

Benzyl alcohol purchased from E. Merck, India was used without further purification and 2,2,6,6-tetramethylpiperidine-N-oxyl(TEMPO) was purchased from Aldrich (USA). Solvent used was of reagent grade. Gas chromatographic analysis was done by using a Varian 450-GC instrument equipped with an FID detector and a CP-Sil 8 CB capillary column.

4.2.2 Catalytic reaction

The aerobic oxidation of benzyl alcohol was carried out in a 25 mL two necked round bottomed flask equipped with a magnetic stirrer and condenser which was immersed in a
temperature controlled oil bath. A balloon filled with oxygen was fitted to the top of the condenser. The substrate benzyl alcohol was mixed with 10 ml acetonitrile (CH$_3$CN) solvent followed by the addition of copper complex (1 mol%) and TEMPO (5 mol%) (Scheme III). The reaction suspension becomes greenish and the reaction is carried out at 80°C. Samples of the reaction mixture were taken out regularly and analyzed by gas chromatograph (GC). This catalytic oxidation of benzyl alcohol mainly results in the formation of the product benzaldehyde and no other products as confirmed from GC.

C$_6$H$_5$OH

1 mol% catalyst, 5 mol% TEMPO
CH$_3$CN (10ml), 80°C

C$_6$H$_5$CHO

Scheme III

4.3 RESULTS AND DISCUSSION

The oxidation of benzyl alcohol has been chosen as the model reaction to test the catalytic potential of long chain copper(II) dimeric carboxylate complexes for aerobic oxidation of alcohols. It has been known from the literature that this type of complexes has not been used as catalyst for alcohol oxidation under aerobic conditions in presence of TEMPO as the cocatalyst. Therefore, our aim was to compare the catalytic activity of these long chain copper complexes ligated to substituted pyridine ligands with that of other dimeric paddle wheel copper complexes that were earlier synthesized in our lab. The results are listed in Table 4.1.
Table 4.1. Results of benzyl alcohol oxidation under aerobic condition using Cu-TEMPO catalytic system in presence of atmospheric oxygen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (1 mol%)</th>
<th>Time (h)</th>
<th>% Conv. of Benzyl alcohol</th>
<th>% Sel. To Benzaldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Cu₂(μ-O₂CC₇H₁₅)₄(4-CNpy)₂] (Ib)</td>
<td>24</td>
<td>No conv.</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>[Cu₂(μ-O₂CC₇H₁₅)₄(3-CNpy)₂] (IIb)</td>
<td>24</td>
<td>No conv.</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>[Cu₂(μ-O₂CC₇H₁₅)₄(4-Mepy)₂] (IIIb)</td>
<td>12</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>[Cu₂(μ-O₂CC₆H₅)₄(4-Mepy)₂] (IV)</td>
<td>16</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>[Cu₂(μ-O₂CC₆H₅)₄(4-Etpy)₂] (V)</td>
<td>24</td>
<td>38</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>[Cu₂(μ-O₂CCH₃)₄(4-Mepy)₂] (VI)</td>
<td>24</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>[Cu₂(μ-O₂CC₆H₅)₄(4-DMAP)₂] (VII)</td>
<td>24</td>
<td>6</td>
<td>100</td>
</tr>
</tbody>
</table>

**Reaction conditions:** Substrate = 5 mmol, Cu(II) catalyst = 1 mol%, TEMPO = 5 mol%, MeCN = 10 ml, Temperature = 80ºC. Products were analyzed by GC.

Poor conversions are obtained with catalysts V, VI and VII (entries 5, 6 and 7) after carrying out the reactions for 24 hours at 80ºC whereas with catalysts Ib and IIb, no conversions (entries 1 and 2) of benzyl alcohol was obtained under identical reaction conditions. However, promising results are obtained with catalysts IIIb and IV which shows remarkable oxidation of benzyl alcohol providing not only 100% selectivity but also 100% conversion (entries 3 and 4). Although the catalysts V, VI and VII show poor conversions but they also have 100% selectivity. From the table, it can be seen that the dimeric long chain copper complexes having cyanopyridine ligands showed no conversion of benzyl alcohol at
all when monitored upto 24 hours. While copper complexes with methylpyridine, ethylpyridine and N,N-dimethylpyridine ligands can catalyze oxidation of benzyl alcohol whether it is having long or short chain aliphatic or aromatic carboxylates. It may be due to the differences in inductive effects of the substituents present in the pyridine ring. It is noteworthy that among all the copper(II) carboxylate complexes, the long chain copper-caprylate-methylpyridine complex, [Cu$_2$(µO$_2$CC$_7$H$_{15}$)$_4$(4-Mepy)$_2$] (IIIb) seems to be the most effective catalyst as it gives the product benzaldehyde with no over oxidation to benzoic acid in least time duration that is 12 hours compared to others. Complexes having aliphatic carboxylates and 4-Mepy ligands, [Cu$_2$(µO$_2$CC$_7$H$_{15}$)$_4$(4-Mepy)$_2$] (IIIb) and [Cu$_2$(µ-O$_2$CCH$_3$)$_2$(4-Mepy)$_2$] (VI) show 100% selectivity to the formation of benzaldehyde and VI has the least efficiency giving only 8% conversion of benzyl alcohol in 24 hours under the same reaction conditions. So, we can assume that the dimeric long chain copper(II) catalyst has higher catalytic efficiency in aerobic oxidation of benzyl alcohol in presence of TEMPO than short chain copper complexes possessing common axial ligands. But we got better results with our previously reported catalysts [Cu$_2$(µ-O$_2$CCMe$_3$)$_4$(4-CNpy)$_2$] and [Cu$_2$(µ-O$_2$CCMe$_3$)$_4$(4-Mepy)$_2$] with 100% selectivity to benzaldehyde in only 3 and 5 hours respectfully under similar reaction conditions. This may be due to the presence of tert-butyl group which is fairly soluble in organic solvents. Again the complex with aromatic carboxylate and 4-Mepy ligand, [Cu$_2$(µ-O$_2$CC$_6$H$_5$)$_2$(4-Mepy)$_2$] (V) has higher percentage conversion (38%) of benzyl alcohol than aliphatic copper(II) carboxylate complex [Cu$_2$(µ-O$_2$CCH$_3$)$_2$(4-Mepy)$_2$] (VI) (only 8%) under similar reaction conditions in 24 hours. All complexes except Ib and IIb show 100% selectivity to benzaldehyde with no over oxidation.
to benzoic acid. Control experiments without either copper(II) complex or TEMPO showed no conversion of benzyl alcohol. Complex \([\text{Cu}_2(\mu-O_2\text{CC}_7\text{H}_{13})_4(4\text{-Mepy})_2]\) (IIIb) showed the best result with 100% conversion of benzyl alcohol to benzaldehyde in 12 hours. Gao et al. also reported a mononuclear Cu(II) catalyst for aerobic oxidation of benzyl alcohol to benzaldehyde in water where they used TEMPO (5 mol%), \(\text{H}_2\text{O}_2\) (1 mL 30%) in presence of 25 mol% of base \(\text{K}_2\text{CO}_3\) resulting 99% conversion of benzyl alcohol in 24 hours.\(^{41}\) We were able to carry out the same using only TEMPO in a better conversion rate of 100% of benzyl alcohol to benzaldehyde in 12 hours without addition of \(\text{H}_2\text{O}_2\) and any bases (Table 4.1, entry 3). So, our catalysis procedure provides economical benefit and simplified procedure in comparison with previously reported systems for aerobic oxidation of benzyl alcohol.

We tried to find a plausible mechanism for the reaction from the UV measurement data. There is a plausible formation of piperidinyloxy copper(II) complex (1) via one electron oxidation of Cu(I) by TEMPO as shown in Scheme IV which is consistent with the UV experiments as suggested by Sheldon et al.\(^{23}\) The UV-vis spectra of our experiment were exactly similar to the patterns shown by Sheldon et al. (Figure 1) based on which we can probably draw a conclusion that our reaction follows the same mechanistic pathways as in their reaction.
Figure 1 (a) UV-vis spectra of (1) TEMPO, (2) Cu(II) complex (3) Reaction mixture
(b) UV-vis spectra of Cu(I)(OAc)–TEMPO (■); Cu(II)(OAc)₂ (▲); TEMPO (●); Cu(I)(OAc) (▲) in acetonitrile under an inert atmosphere (Sheldon’s experiment)²³

Scheme IV

The schematic representation of the reaction mechanism for reaction is illustrated in Scheme V in which a key step is the Cu-centred dehydrogenation of the alcohol followed by reoxidation of Cu(I) by TEMPO to Cu(II) and formation of TEMPOH. Oxygen reoxidizes TEMPOH to TEMPO.
In summary, an effective and selective aerobic oxidation procedure of benzyl alcohol to benzaldehyde using dimeric copper(II) carboxylate complexes having long chain alkyl groups as catalyst in combination with TEMPO as a co-catalyst has been developed. Using the presently developed method, it has been possible to achieve the selective formation of the desired aldehyde product without the use of an added base. The complex [Cu₂(μ-O₂CC₇H₁₅)₄(4-Mepy)₂] (IIIb) has shown the best result with 100% conversion of benzyl alcohol to benzaldehyde in 12 hours. Apparently, improved solubility resulting from the long chain alkyl groups in the catalysts is beneficial in the development of effective catalysts for the oxidation of alcohols.
4.5 References


