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Investigation of 3d-transition metal acetates in the oxidation of substituted dioxolene and phenols

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ABSTRACT

Enzymatic reactions have inspired many chemists to design small molecule mimics that would perform the function of the enzymes in aqueous and or non-aqueous medium. Catechol oxidase (CO) and phenoxazinone synthase (PHS) are two multi-copper enzymes in nature, which has led to model complexes of Mn, Fe, Co, Ni, Cu. Based on our earlier work in this area we have probed the commercially available metal acetates of the above metals to establish a trend in reactivity for catalytic conversions similar to those of the two enzymes. The results show that Mn is the best 3d transition metal for similar catalysis. Mn^{II} acetate was found to convert 3,5-di-*tert*-butylcatechol (DTBC) to 3,5-di-*tert*-butylquinone (DTBQ) with a k_{cat} of $1.3(1) \times 10^3\ h^{-1}$ and for *o*-aminophenol (OAP) to 2-aminophenoxazinone (APX) conversion the $k_{cat} = 111(2)\ h^{-1}$, demonstrating efficient CO and PHS like activity. Kinetic studies show that DTBC oxidation follows a first order kinetics with respect to the substrate for each of those metal(II) acetates with activity order of Mn » Co > Cu > Fe ≥ Ni. Through mechanistic investigation we found that the reactive oxygen species detected during the oxidation of DTBC is mostly hydroxyl radical for Mn, Fe and Co whereas Cu and Ni generate H_2O_2.

1. Introduction

Bio-oxidation reactions have inspired the design of a library of metal complexes, which led to many successful functional models of enzymes over the past few decades [1–5]. These complexes have gained importance for their ability to shed insight on the mechanistic pathways of the original enzymes. Many of these are also considered as efficient catalysts in spite of their activity being much less in comparison to the enzymes. The advantage of the small molecule mimics are that they are capable of doing the reactions in organic solvents. Metalloenzymes can catalyze the conversion of organic compounds with molecular oxygen under physiologically mild conditions [6–10] but they are not capable of performing in organic solvents unless specially modified. Therefore, the design and synthesis of transition metal complexes and having ability to activate molecular oxygen is an attractive approach to green oxidation catalyst based on bio-inspired concept.

Among the various catalytic conversions carried by enzymes we chose the ones similar to that carried by catechol oxidase (CO) and phenoxazinone synthase (PHS), two copper containing metalloenzymes in nature that inspired us and many other bio-inorganic chemists to design model complexes. CO oxidizes catechols/dioxolenes to corresponding quinones. Quinone based molecules are found to be useful to design compounds used to suppress bone marrow function, inhibit proteases, and generate anticancer agents. Naturally occurring quinones like metachronin, bolinaquinone are potent anticancer agents [11,12]. Quinones are also useful scavengers of mercaptans, sulfides, cyanides and amines [13]. PHS catalyzes the oxidative coupling of substituted 2-aminophenol to 2-aminophenoxazinone chromophore (Scheme 1) known as actinomycin, a well known antineoplastic agent [14]. Among various approaches to utilize the properties of enzymes in different ways, attempt to fix the enzymes on surfaces and perform organic transformations through heterogeneous catalysis is one of them [15–19]. However, binding enzymes to a solid state support are tedious and may not always work in organic solvents for similar transformations. We attempt to involve commercially available metal acetates to perform organic transformations similar to CO and PHS (Scheme 1) in laboratory conditions in organic solvents due to their potential in pharmaceutical, dyes and other industrial purposes.

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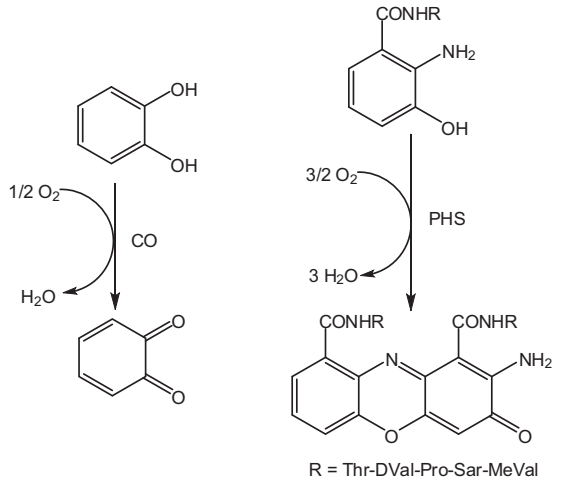


Scheme 1. Oxidation reactions catalysed by catechol oxidase (CO) and phenoxazinone synthase (PHS).

Researchers around the world have put significant effort to model CO and PHS through design of metal complexes of complicated ligand systems [20–23] and provided insight about the mechanistic pathway [21,22,24–26] of these enzymes. The metal salts, especially the acetates which are used as precursor in syntheses of many such biomimetic complexes are scarcely probed for their efficiency in such catalysis [27–30]. At first it seems quite reasonable, since the coordinating atoms and the geometry of the enzyme active site are not related to the structure of metal acetates in any way. However, since the metal salts have been ignored, the role and influence of the metal ion as standalone remained unexplored. One may also argue that probing metal acetates is essential since it would inform us that how much the mechanistic pathway or the ROS generated may be influenced by the ligand when complexed with the metal. During our efforts in this area we happened to obtain a Mn^{III} complex, which provided the best turnover for DTBC oxidation and it had —OR type oxygen donors [31]. The above result led us to think that metal acetates needs to be investigated for their efficiency in DTBC oxidation. To begin this chase, since our success was with a Mn^{III} complex, hence Mn^{III}-acetate was our obvious first choice to probe for CO and PHS activity. The results were promising. Mn^{III} acetate demonstrated itself to be one of the best small molecule mimics for PHS using 2-aminphenol (OAP) as substrate to form 2-aminophenoxazinone (APX) and an efficient CO mimic with a turnover of the order of $10^3\ h^{-1}$ for oxidation of 3,5-di-*tert*-butylcatechol (DTBC) to 3,5-di-*tert*-butylbenzoquinone (DTBQ) [32].

However, we still did not know about the activity of the rest of the metal ions frequently used for the syntheses model complexes of CO or PHS. Hence, we probed a series of 3d-transition metal acetates for DTBC and OAP oxidation. The metals were chosen from the list of 3d-metals used so far to design mimics of CO or PHS using different ligand systems *viz.* copper [24,33–54], iron [25,55–57], cobalt [58–65], manganese [66–79], nickel [26,68,80–83] and zinc [33,84]. PHS mimics cannot be found as much as CO but yet are well studied with 3d-metals *viz.* Co [85–92], Mn [71,89,91,93], Cu [94], Fe [91,95] complexes using 2-aminophenol as substrate. We investigated the possible reactive oxygen species (ROS) involved for each of the metal ions. We chose metal acetates over chlorides or nitrates since the acetates are labile ligands, commercially available and solvent compatible with DTBC and OAP.

The comparative study of Mn^{II}, Fe^{II}, Co^{II}, Ni^{II} and Cu^{II} is presented here for three type of oxidation reactions which are oxidation of DTBC to DTBQ, OAP to APX and oxidative C—C bond coupling of 2,6-di-*tert*-butylphenol (2,6-DTBP) to 3,3′-5,5′-tetra-*tert*-butyldiphenoquinon (DPQ). We found that although Cu^{II} happens to be the metal of choice in the enzymes CO and PHS. In laboratory among the metal acetates, $Mn^{II/III}$-acetate is the most efficient. Co^{II}- and Cu^{II}-acetate seems to be next in line with similar k_{cat} for oxidizing DTBC to DTBQ but the ROS species involved in the processes are different. In conversion of OAP to APX, $Mn^{II/III}$ again seems to be the best among the 3d-transition metal ions and the activity of Cu^{II}-acetate is comparable with Fe^{II}- and Co^{II}-acetate. Probing the active species during DTBC oxidation showed that the DTBC also act as ligand and the acetates are all stripped of from the metal ion during catalysis.

2. Experimental

2.1. Materials and methods

All reactions were carried out using HPLC grade solvents [methanol (Merck), acetonitrile (Merck)]. All metal(II) acetate [*e.g.*, manganese(II) acetate tetrahydrate, iron(II) acetate, cobalt(II) acetate tetrahydrate, nickel(II) acetate tetrahydrate, copper(II) acetate monohydrate], 3,5-di-*tert*-butylcatechol, dimethylsulfoxide (DMSO), (±)-α-tocopherol, probucol, D/L-*p*-chlorophenylalanine, 2-aminophenol, potassium titanium oxide oxalate dihydrate were all purchased from Sigma and used without further purification. 3,5-di-*tert*-butylbenzoquinone was also purchased from Aldrich and used to calculate molar extinction coefficient (ϵ) in 90:1 acetonitrile, methanol mixture. L-methionine, L-histidine [SRL (India)] and sodium hydroxide [Merck (India)] were also used as received. Methyl ester of methionine and histidine were synthesized according to a previously reported literature procedure [96]. NMR spectra were recorded on Bruker Avance III 500 MHz or on Jeol ECS400 MHz spectrometer at room temperature (25 °C). Electronic spectra were recorded using Varian Cary 300 Bio UV–vis spectrophotometer. Electrospray ionisation mass spectra were recorded using micromass Q-Tof *micro*™ (Waters) by positive and also negative mode electrospray ionization. X-Band EPR spectra were recorded on a Bruker BioSpin WinEPR spectrometer.

2.2. Catalytic oxidation of DTBC

UV–vis spectra for kinetic studies were recorded by using a quartz cuvette (1.0 cm path length) and a Varian Cary 300 Bio UV–vis spectrophotometer equipped with a Peltier thermostating accessory. All the kinetics measurements were conducted at a constant temperature of 25 °C, monitored with a thermostat. DTBC in acetonitrile were added to the solutions of M^{II}-acetate in methanol under aerobic condition at room temperature (25 °C). The final ratio of acetonitrile:methanol in cuvette was 90:1 v/v. Absorbance *vs.* wavelength plots were generated for these reaction mixtures, recording spectrophotometric data at a regular time interval of 5 min in the range 300–700 nm. To determine the substrate concentration dependence of the rate and various kinetic parameters, 10^{-4}–10^{-6} M solutions of catalyst was treated with 100–800 M equivalents of DTBC and the absorbance monitored as mentioned above. For Mn^{II}-acetate kinetic experiments were performed using 10^{-6} M catalyst concentration while other metal acetates are not active at such low concentration. Hence for Co^{II} and Cu^{II} acetate we used 10^{-5} M concentration while for Fe^{II} and Ni^{II} acetate even higher concentration (10^{-4} M) of catalyst were used. The kinetic parameters were determined by using Michaelis–Menten, Lineweaver–Burk and Eadie–Hofstee plot. The product (DTBQ) was also characterized by ESI–MS and NMR spectroscopy. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.93$ (d, 1H, $J = 2.28$ Hz),

6.21 (d, 1H, J = 1.52 Hz), 1.26 (s, 9H), 1.22 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.26 (C-1), 180.17 (C-2), 163.46 (C-3), 150.07 (C-4), 133.60 (C-5), 122.22 (C-6), 36.16 (C-7), 35.61 (C-8), 29.34 (C-9), 28.01 (C-10) ppm. ESI–MS positive ion mode: m/z = 243.14 [(DTBC + Na^+)]$^+$ (calc. 243.14). The data showed that only DTBQ is formed from DTBC. No other side product is obtained.

2.3. Detection of hydrogen peroxide in the catalytic reaction of oxidation of DTBC

The formation of hydrogen peroxide during the catalytic oxidation of DTBC was probed by two different methods-

H_2O_2 can be detected by the generation of characteristic peak at 352 nm for I_3^- ion with potassium iodide. To detect hydrogen peroxide after the oxidation of DTBC, DTBC was oxidized by 1 mol% M^{II} acetate for 2 h in acetonitrile and methanol mixture. The formed DTBQ was then extracted three times using dichloromethane. Water part was then acidified to pH 2 using diluted H_2SO_4 and one-third volume of KI solution (500 mg/10 mL) in water was added to it with 100 nM Horse Radish Peroxidase and the appearance of the band at 352 nm characteristic for I_3^- ion was monitored. Control experiments were performed using only H_2O_2 solution and atmospheric oxygen (without catalyst or DTBC).

H_2O_2 formation can also be detected by formation of Ti^{IV}-peroxo species using potassium titanium(IV) oxalate. In this experiment the catalytic reaction of DTBC oxidation and the extraction procedure was same as the above method. The isolated aqueous part was added 1 mM solution of potassium titanium(IV) oxalate to monitor the band ca. 379 nm, due to the formation of Ti^{IV}-peroxo bond [97,98]. Control experiment was also performed using hydrogen peroxide.

2.4. Catalytic oxidation of 2-aminophenol (synthesis of 2-aminophenoxazinone or APX)

Oxidation of *o*-aminophenol (OAP) was carried out by taking OAP (109.0 mg, 1.0 mmol) and M^{II} acetate (0.01 mmol) (M^{II} = Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}) in methanol and then the reaction mixture was stirred for 12 h. Pure product precipitated out of the solution which was filtered, collected. The product was characterized by ESI–MS, ^{1}H NMR and ^{13}C NMR. ESI–MS (+ve ion mode): m/z = 213.08 [(APXH)]$^+$ (calc. 213.07); m/z = 235.05 [(APXNa)]$^+$ (calc. 235.05); m/z = 251.03 [(APXK)]$^+$ (calc. 251.02). ^{1}H NMR (500 MHz, Me_2SO-d_6): δ = 7.71 (dd, 1H, J = 7.5 Hz, ArH), 7.44 (m, 2H, ArH), 7.39 (m, 1H, ArH), 6.80 (br, s, 2H, NH_2), 6.36 (s, 2H, ArH) ppm. ^{13}C NMR (125 MHz, Me_2SO-d_6) δ = 180.2 (C-3), 148.9 (C-10a), 148.2 (C-4a), 147.3 (C-2), 141.9 (C-5a), 133.7 (C-9a), 128.8 (C-7), 127.9 (C-9), 125.3 (C-8), 115.9 (C-6), 103.4 (C-1), and 98.3 (C-4) ppm.

Kinetics of the aerobic oxidation of OAP to APX in presence of Mn^{II} acetate were measured by monitoring the change in absorbance as a function of time at 430 nm ($\epsilon = 22 \times 10^3$ $M^{-1}cm^{-1}$), which is characteristic of 2-aminophenoxazin-3-one. All the kinetics measurements were conducted at a constant temperature of 25 °C, monitored with a thermostat. To determine the substrate concentration dependence on the rate and various kinetic parameters, 5 μM solutions of catalyst was treated with 500, 1000, 1500, 2000, 2400, 3000, 3200 and 3400 M equivalents of OAP and the absorbance monitored as mentioned above. Absorbance *vs.* wavelength plots were generated for these reaction mixtures, recording spectrophotometric data at a regular time interval of 5 min in the range 300–700 nm. The final ratio of acetonitrile:methanol in cuvette was 90:1 v/v. The kinetic parameters were determined by using Michaelis–Menten plot and Lineweaver–Burk plot.

Table 1
Kinetic parameters for the oxidation of DTBC to DTBQ.

[Cat]	V_{max} [M min^{-1}]	Std. error	K_M [M]	Std. error	k_{cat} [h^{-1}]
Mn^{II} acetate	2.2×10^{-5}	1.67×10^{-6}	0.00066	9.25×10^{-5}	$1.3(1) \times 10^3$
Fe^{II} acetate	1.4×10^{-5}	9.86×10^{-7}	0.00714	8.54×10^{-4}	8.4(2)
Co^{II} acetate	5.6×10^{-6}	1.96×10^{-6}	0.010	5.39×10^{-3}	$0.32(1) \times 10^2$
Ni^{II} acetate	1.4×10^{-5}	4.46×10^{-7}	0.00302	2.25×10^{-4}	8.4(3)
Cu^{II} acetate	4.03×10^{-6}	9.79×10^{-7}	0.00015	1.26×10^{-5}	$0.23(1) \times 10^2$

2.5. Oxidative CC coupling of 2,6-di-tert-butylphenol (conversion of 2,6-di-tert-butylphenol to 3,3′-5,5′-tetra-tert-butyldiphenoquinone)

Oxidative coupling of 2,6-di-*tert*-butylphenol (2,6-DTBP) was performed by taking 2,6-DTBP in methanol, sodium hydroxide in water was added to it such that the overall concentration is 10 mol%. To the above solution M^{II} acetate (0.01 mmol) (M^{II} = Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}) in methanol was added and the mixture was stirred at 25 °C for 4–24 h. Product started forming as red precipitate after an hour of addition of M^{II} acetate solution. On completion of the reaction the product was collected by filtration, washed by methanol and dried. The product was found to be pure by TLC and hence the dried product was analyzed by ESI–MS and ^{1}H NMR spectroscopy. ESI–MS (positive ion mode): m/z = 409.30 [(DPQH)]$^+$ (calc. 409.31); m/z = 431.29 [(DPQNa)]$^+$ (calc. 431.29). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71(s, 4H), 1.36 (s, 36H) ppm.

2.6. Mass spectrometry

ESI mass spectrometric data were recorded using Waters Q-Tof micro mass spectrometer. The mass spectrometric studies of catechol oxidation were performed using (1:1) acetonitrile, methanol mixture. The ESI–MS was performed with 1:50 mixture of M^{II}-acetate with DTBC having M^{II}-acetate in 10 μM concentration. Higher catalyst ratio was used to obtain good signal to noise ratio for the various metal bound species formed. The ESI–MS of the catalytic products were also performed with 10 μM stock solutions.

3. Results and discussion

3.1. Catecholase activity studies

Catechol oxidase (CO) is a dinuclear Cu^{II} containing enzyme having a type-3 active site [99], which catalyzes the oxidation of catechol to quinone. The structural and functional aspects of CO have been elucidated with the help of several model systems [24,49,68,71,81,82,84,100–102]. In addition the search for the mimics leads to several alternate mechanisms of oxidation [20–22,46,103–105]. In model studies on catecholase activity, DTBC is usually used as the substrate since the bulky groups prevent over oxidation such as ring opening [106–108] and also show prominent increase in absorbance at *ca.* 400 nm with increase in the formation of oxidized species (DTBQ).

We performed kinetic and mechanistic studies of DTBC oxidation using 10^{-4}–10^{-6} M solutions of six transition metal acetates as mentioned earlier. We found that among six metal acetates we tried, only Zn^{II} acetate was inactive whereas the other five (Mn^{II}, Fe^{II}, Co^{II}, Ni^{II} and Cu^{II}-acetate) were active. The redox inactive Zn^{II} acetate is supposed to be catalytically inactive, which corroborates our result. For a particular catalyst–substrate mixture the rates were calculated from the initial slope of ΔA *vs.* time plots (change in absorbance at 400 nm), using up to 800 M equivalent of DTBC and analyzed by Michaelis–Menten equation, Lineweaver–Burk and Eadie–Hofstee plot [109] (Table S1 and Fig. S1) and the purity of the product DTBQ was further confirmed by NMR and ESI–MS studies (Figs. S2–S4). In all the three cases the kinetic parameters obtained

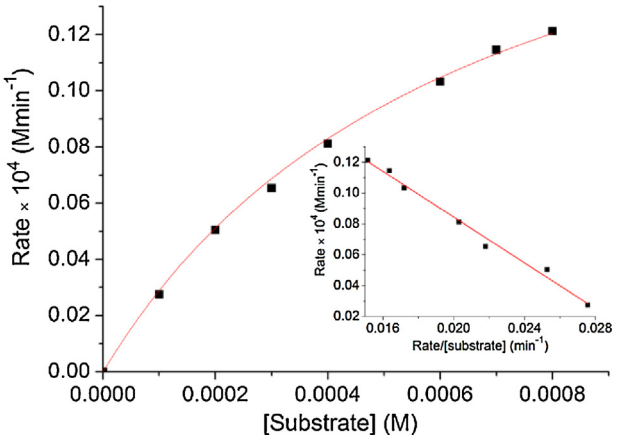


Fig. 1. Plot of initial rate *vs.* substrate concentration for the oxidation of DTBC catalysed by Mn^{II} acetate. The inset shows Eadie–Hofstee plot.

are in good match with each other. Based on the three fitting data the turnover number (k_{cat}) and other kinetic parameters are shown in Table 1 which reflects that Mn^{II} acetate is the most efficient catalyst among them with a k_{cat} of $1.3(1) \times 10^3\ h^{-1}$ (Fig. 1). The k_{cat} of Mn^{II}-acetate is better than majority of designed mimics and of the same order as that of Mn^{III}-acetate ($k_{cat} = 1.72(2) \times 10^3\ h^{-1}$) [32] reported by us earlier. This suggests that Mn is the most efficient among 3d-transition metals for this particular purpose. Nature did not redeem Mn fit for this purpose and rather chose Cu although the abundance of Mn is more than copper in earth crust or in sea bed [110,111]. One reason might be that it is difficult for nature to incorporate Mn in that ligand environment and direct its function to specifically oxidize catechol.

In fact the $Mn^{II/III}$ acetate is known to perform other oxidation reactions as well [112–115]. Hence the differences in electronic properties of the two metal ions *viz.* redox potential, stabilization of a certain geometry rendered by the protein, ability to perform other reactions led to the choice of Cu. The results emphasize that being efficient as a metal ion for a certain purpose and mere abundance does not necessarily render it suitable by nature for incorporation into a proteins active site. Nature has chosen Cu^{II} for the active site of CO although Cu^{II} acetate ($k_{cat} = 0.2(1) \times 10^2\ h^{-1}$) is less active than Mn^{II} acetate ($k_{cat} = 1.3(1) \times 10^3\ h^{-1}$). On the other hand Cu^{II} acetate and Co^{II} acetate ($k_{cat} = 0.3(1) \times 10^2\ h^{-1}$) have similar k_{cat} for the CO activity but the K_M values are different. The ratio of k_{cat}/K_M actually predicts the best catalyst for a bio-mimetic reaction [35,45,52]. In our case the calculation shows that $Mn^{II/III}$ has k_{cat}/K_M value of the order of $10^6\ M^{-1}\ h^{-1}$ and the next best one is the nature's choice Cu^{II} with a k_{cat}/K_M of $10^5\ M^{-1}\ h^{-1}$. The other 3d-metals (Fe, Co, Ni) probed are at least two order of magnitude less than Cu^{II}-acetate. It appears that although there are many excellent Ni^{II} catalysts for CO activity but in case of Ni^{II} the importance of the ligand is very much appreciated since Ni^{II} acetate by itself has a very low turnover number even at 10^{-4} M concentration (Table 1). Fe^{II}-acetate also has a low k_{cat} even at 10^{-4} M concentration and it appears from the literature that there has not been much attempts to use Fe^{II} based complexes as mimics of CO [25,55–57]. $Fe^{II/III}$ seems to be a better choice for catechol dioxygenase (which leads to intradiol or extradiol cleavage) based on the literature data [116–123]. Hence, the two metal ions Mn and Cu may provide a good example to demonstrate how the 'rule of fitness' may lead to rejection of a metal ion in an enzyme active site.

In this work, we do not intend to say that the metal acetates are specific to a catalytic reaction. In fact we know that metal acetates used in this work are also known to catalyze many other reactions. Our results demonstrate that how metal acetates can be effectively performing a reaction similar to enzyme and may help us choose the metal to perform a similar reaction in the laboratory. The metal acetates also provide more insight about the rationality of the choice of metal at the enzyme active site based on their redox activity for a particular reaction. This reactivity knowledge may be used to design better bioinspired catalyst to perform similar reactions. A point to note is that not all proteins/enzymes are selective *in vitro*. Enzymes without specific condition and coordination environment around them might be non-selective *viz.* xanthane oxidase can generate superoxide in presence of oxygen [124,125], haloperoxidase can catalyze sulfoxidation [126], tyrosinase can perform catecholase activity [127,128] and phenoxazinone synthase activity [127,128], laccase can also perform phenoxazinone synthase activity [129,130], nitrogenase can reduce unsaturated hydrocarbon substrates, cyanate, thiocyanate [131,132]. Although most model complexes of the enzyme CO are copper complexes but a close look at the Mn complexes show that the Mn complexes exhibit good catalytic efficiency which is overall better than any other probed metal complexes suggesting that Mn is the best for similar activity in laboratory or in industry.

Table 2
Percentage (%) of inhibition of DTBC oxidation catalysed by M^{II} acetates (M^{II} = Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}). The mean of two independent experiments are tabulated (less than 10% inhibition is neglected).

Inhibitor	Mn^{II} acetate	Fe^{II} acetate	Co^{II} acetate	Ni^{II} acetate	Cu^{II} acetate
(±)-α-Tocopherol	None	None	None	None	None
probucol	None	15(3)	16(4)	None	None
DMSO	65(3)	22(2)	29(3)	None	None
methionine ester	100	100	100	100	100

3.2. Inhibition of catecholase activity

The mechanistic pathway for DTBC oxidation was probed for all the active metal acetates used. An important part of the mechanistic pathway is the type of ROS involved in the catalytic process. We used different inhibitors in the reaction mixture to check their effect on the reaction rate which in-turn provided insight into the possible ROS involved. In general we have used 10 M equivalent of the inhibitor with respect to the catalyst concentration. The inhibitors used in the catalytic oxidation of DTBC are (±)-α-tocopherol (singlet oxygen quencher) [133,134], probucol (peroxide and superoxide quencher) [135,136] and DMSO (hydroxyl radical inhibitor). The effects of those inhibitors are shown in Table 2 (Fig. S5). One common result for all the metal acetates is that amino acids inhibit the catechol oxidation ability *viz.* use of 10 M equivalent of methyl ester of methionine or methyl ester of histidine showed complete inhibition of oxidation of DTBC. This is in good agreement with our earlier studies with other CO model complexes which suggested that the amino acids or methyl esters of amino acids are potential inhibitors of catechol oxidation as they compete with the substrate (DTBC) and or oxygen for binding to the catalyst and inhibit the oxidation process [31,32,137].

3.3. Evaluation of the ROS species

During oxidation of DTBC when the metal is reduced, the presence of molecular oxygen would lead to oxidation of the metal ion where the oxygen is converted to an ROS. However, depending on the number of electrons available for the ROS it may be converted to water or stay as hydrogen peroxide. Out of the major mechanistic pathways established the one which produces two molecules of quinone and water is the most accepted one for the enzyme catechol oxidase. However, there are only

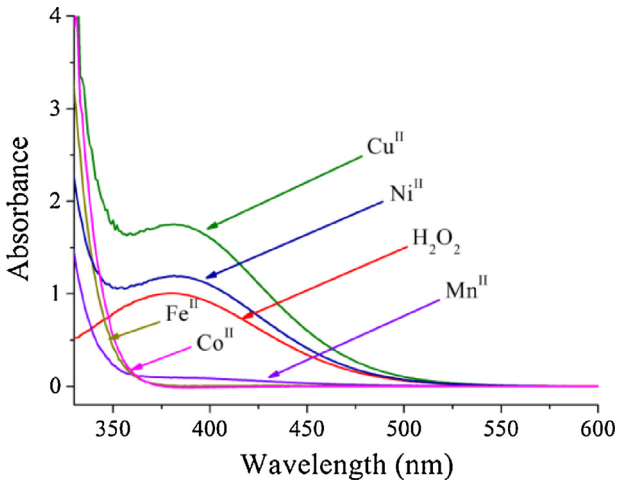


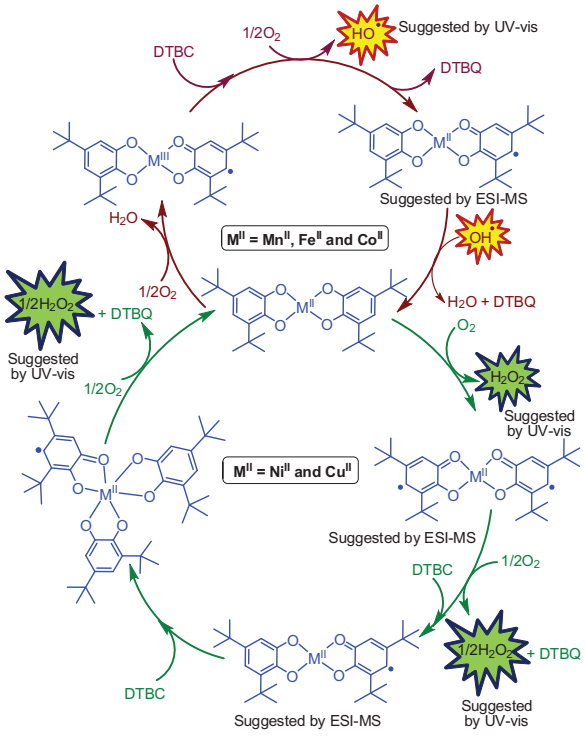
Fig. 2. UV–vis spectra of hydrogen peroxide detection test showing characteristic peak at around 379 nm for the generation of Ti^{IV}-peroxo complex by H_2O_2 in presence of potassium titanium(IV) oxalate. The spectrum for control using H_2O_2 as standard is also shown.

few model systems which follow this pathway [138–141]. Most designed complexes that catalytically perform catechol oxidation are known to perform the oxidation through alternate pathway which involves production of quinone along with H_2O_2 rather than water [24,34–36,52,53,76,140,142–145]. Presence or absence of hydrogen peroxide as end product in our cases were tested by using KI solution and Horse Radish Peroxidase [53,140] and also using potassium titanium(IV) oxalate [97,98].

For Cu^{II} and Ni^{II} acetate hydrogen peroxide was detected as the side product of DTBC oxidation, while for other three acetates (Mn^{II}, Fe^{II} and Co^{II}) H_2O_2 was not detected as an end product (Fig. 2 and S6). Literature survey showed that formation of H_2O_2 largely depends on the metal centre involved in the catalytic process. In most of the model studies the ROS detection tests were not performed as per the literature data but in cases where it has been performed, a trend appears. $Mn^{II/III/IV}$ systems always produce water not H_2O_2. It may be argued that Mn would decompose H_2O_2 [76] hence it cannot be detected but then we have detected peroxide for Mn based catalyst earlier [31]. For $Ni^{II/III}$ CO mimics, H_2O_2 is always found to be the end product of DTBC oxidation [26,80–82,146] and the same is true for model complexes of Cu also [24,53]. Co and Fe complexes are also known to decompose H_2O_2 [147–150]. Although we do not get H_2O_2 as an end product but our mechanistic studies using UV–vis spectroscopy in presence of inhibitors show that probucol inhibits the conversion of DTBC to DTBQ by Fe^{II} and Co^{II} by ca. 15%, suggesting that peroxo intermediate is generated which may get consumed by the metal center. Though there are a few Cu^{II} model complexes, which report the production of water during oxidation of DTBC but the predictions were made without any experimental evidences [103,138]. Hence, it seems that as per our studies and the literature evidences, Cu^{II} and Ni^{II} generate H_2O_2. Mn generates H_2O and Fe and Co generates H_2O_2 which decomposes fast in presence of the metals and cannot be detected. The results indicate the importance of the protein coordination in changing the mechanistic pathway *viz.* although Cu^{II} generates H_2O_2 in most of the CO model complexes and as acetate [24,34–36,52,53,140], in the protein active site it is known to generate water [21,103].

3.4. Speciation during catalysis

The EPR studies show weak signal at $g \approx 2.00$ during oxidation of DTBC for Mn^{II}, Fe^{II}, Co^{II}, Cu^{II} acetates (Fig. S7). The



Scheme 2. Plausible mechanism of DTBC oxidation.

signal is characteristic of formation of organic radical species (semiquinone of DTBC) as the reaction intermediate during the catalytic process. The literature data is also in good agreement with our studies, suggesting formation of a semiquinone intermediate [20,26,61,62,67,80,137,146,151] in presence of the 3d-metals used in those complexes.

In order to get further insight into the nature of possible intermediates, electrospray ionization mass spectral (ESI–MS) studies in negative ion mode were performed with the catalytic reaction mixture of M^{II} acetates and DTBC (1:50) in methanol. ESI–MS spectra were recorded within 5 min of mixing a M^{II} acetate and DTBC. The observed and simulated patterns are shown in Figs. S8–S13. Formation of similar species were observed in all cases, where two DTBC units were attached to the metal centre as $[M^{II}(DTBC)(DTSQ)]^-$. The data suggests that in solution the metal acetates render monomeric metal-DTBC complexes which help catalyze the DTBC to DTBQ. Hence the substrate also acts as ligand in solution. ESI–MS being a soft technique when used carefully seems to provide useful data on the reaction solutions. We opted for ESI–MS negative mode since the substrate was a di-negative catechol which can provide multiple binding to a metal ion of di-positive charge and hence the resultant species is supposed to be negative.

Once we combine the evidences obtained from UV–vis studies, ESI–MS and EPR, the results suggest that Mn, Fe and Co oxidizes DTBC in presence of oxygen through generation of hydroxyl radical whereas Ni and Cu oxidizes DTBC through generation of hydrogen peroxide. Hence we propose the mechanistic pathway where the metal form a bis/tris chelate with the substrate followed by which the substrate gets oxidized to quinone and then leaves the metal centre. In this way the substrate also acts as a ligand and forms the active catalytic species by replacing the labile acetates (Scheme 2). EPR studies provide evidence of organic radical, a semiquinone intermediate and hence our proposition in all the cases, except Ni. Ni^{II} is very slow reacting due to which the amount of semiquinone intermediate at any time may not have been enough to obtain a good signal in EPR. Manganese appears to be different from the other metal ions investigated in this work.

Table 3
Oxidation of OAP to APX using M^{II} acetates (M^{II} = Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}).

[cat]	Solvent	Time [h]	% Yield[a]
Mn^{II} acetate	CH_3OH	12	60(4)
Mn^{II} acetate	H_2O	12	35(5)
Fe^{II} acetate	CH_3OH	12	32(2)
Co^{II} acetate	CH_3OH	12	28(2)
Ni^{II} acetate	CH_3OH	12	00
Cu^{II} acetate	CH_3OH	12	26(2)
No catalyst	CH_3OH	24	00

Reaction conditions: OAP (1 mmol), catalyst (1 mol%) under air, 25 °C.
[a] Isolated yield.

We earlier found the involvement of Mn^{IV} [32], which was strongly supported by the literature evidences [152–155]. Now in this work when we started with Mn^{II} acetate it seems that the $Mn^{II} \leftrightarrow Mn^{III}$ couple is active during the redox process as per the obtained evidences showing the versatility of Mn in oxidizing DTBC due to the accessible oxidation states.

3.5. Oxidative coupling of 2-aminophenol (OAP)

Synthesis of the phenoxazinone chromophore gained importance in catalysis due to its occurrence as an intermediate in biosynthesis of the antibiotic actinomycin-D by Streptomyces antibioticus using the enzyme phenoxazinone synthase (PHS) [156–160]. Actinomycin-D, acts by inhibiting DNA-directed RNA synthesis and is used clinically for the treatment of certain types of cancer [161–163]. Phenoxazinone containing compounds are also receiving increasing attention for various industrial applications *viz.* as antifungal and antimicrobial agents, dyes [164] and for the development of fluorescent probes for the detection of hydroxy radicals and live cell imaging [130,165–166].

In laboratory oxidative conversion of *o*-aminophenol (OAP) to 2-aminophenoxazinone (APX) has been used as a model for the behaviour of the enzyme PHS. The native enzyme is known to require 4–5 copper centres for maximum activity and less number of copper centres reduces the activity [156]. However, the model complexes of PHS are mostly rather simple mononuclear complexes of transition metal [71,85–95,167]. There is only one report of a tetranuclear Cu^{II} complex as model of phenoxazinone synthase by Mukherjee et al. In that report the ligand is also attributed to be important for the activity due to its redox non-innocent nature [94]. Based on the literature data, it appears that mononuclear metal complexes can model the functional activity of PHS, which is a pentanuclear copper(II) enzyme. In this report we show that without designing of any new ligand and rather using commercially available metal acetates at room temperature we can perform the conversion of OAP to APX or DTBC to DTBQ.

We examined the OAP oxidation ability of Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II} metal acetates. The oxidation reactions were performed using 1 mol% of catalyst in methanol at 25 °C (Table 3) and the end product was characterized and confirmed by NMR and ESI–MS (Figs. S14–S18). Again the activity of Mn^{II} acetate is better than the other metal acetates used in the study. Earlier we found that Mn^{III}-acetate showed the highest turnover among the model complexes of PHS. Now after probing a series of 3d-transition metals which have been used for modelling PHS we find that Mn tops the list. Nature's choice Cu seems to be less active than Mn for the PHS activity than Mn. Mn^{II}-acetate has the ability to convert OAP to APX even in water at room temperature although the yield almost reduces to half (Table 3).

The best performance of Mn led us to perform detailed kinetic studies of its aerobic OAP oxidation to APX, by monitoring the change in absorbance as a function of time at 430 nm ($\epsilon = 22 \times 10^3\ M^{-1}cm^{-1}$, characteristic of 2-aminophenoxazin-3-one). Detailed kinetic studies reveal first order kinetics with respect to substrate (OAP) (Fig. 3) with a k_{cat} value of 111(2) h^{-1}. We also performed some initial investigation on the possible reactive oxygen species (ROS) involved with the OAP oxidation using UV–vis spectroscopy. The studies show that hydroxyl radical may not be involved in this case, unlike the DTBC oxidation, since the reaction rate is not much affected by DMSO, which is a strong inhibitor of hydroxyl radical. The reaction also remains almost unaffected by other ROS quenchers *viz.* (±)-α-tocopherol or probucol (Fig. S19), which suggests that superoxide, peroxide and hydroxyl radical may be excluded. Methionine ester inhibits the reaction completely suggesting that substrate coordination with catalyst is essential for activity. Our earlier work shows that the amino acids or their esters coordinate to the metal centre preventing the reaction with DTBC or oxygen [31,32,137,168].

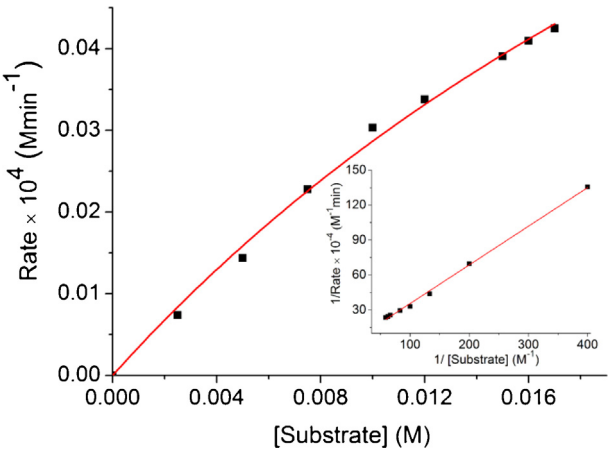


Fig. 3. Plot of initial rate *vs.* substrate concentration for the oxidation of OAP catalysed by Mn^{II} acetate. The inset shows Lineweaver–Burk plot.

The results of this work suggest that Mn may be the best with even oxygen donor ligands for CO or PHS activity. However, nature chose 'Cu' over 'Mn' probably due the 'rule of fitness' for an enzyme site. The environment and suggested geometry around the metal centres in CO or PHS probably did not support the incorporation of $Mn^{II/III}$ due to reduced stability of the bound Mn and its possible ability to switch between at least three oxidation states (II–IV) and perform other reactions using the available articulate ligand environment of the protein.

3.6. Oxidative CC bond coupling of 2,6-di-tert-butylphenol (2,6-DTBP)

Carbon–hydrogen bond activation protocols allow the utilization of a CH bond as a functional group, offering a direct route for the creation of carbon–carbon and carbon–heteroatom bonds. The success of the metal acetates in formation of semiquinone in DTBC and the OAP oxidation and the fact that DTBC attaches to the metal acting as ligand and substrate suggested that it worth making an effort to probe the oxidative coupling of sterically hindered 2,6-DTBP. In general, 3d-transition metals are relatively less popular for activation of carbon–hydrogen bonds compared to 4d and 5d transition metal catalysts (*viz.* Pd, Ru) [169–177]. First-row (3d) transition metals such as Fe, Co, Ni, Mn, or Cu are used relatively rarely [178–184].

Various research groups have studied the oxidation of 2,6-DTBP using molecular oxygen [185–189]. H_2O_2 or ^tBuOOH as oxidant to give two different oxidation products 3,3′-5,5′-tetra-*tert*-butyldiphenoquinone (DPQ) and 2,6-di-*tert*-butylbenzoquinone (BQ) [190,191]. Among the 3d-transition metals, there are more examples of copper [185,186,190,192] and cobalt salts and

Table 4
Oxidation of 2,6-DTBP to DPQ using M^{II} acetates (M^{II} = Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}).

[cat]	Solvent	Time [h]	% Yield[a]
Mn^{II} acetate	CH_3OH/NaOH	04	90(2)
Fe^{II} acetate	CH_3OH/NaOH	24	0
Co^{II} acetate	CH_3OH/NaOH	04	46(3)
Ni^{II} acetate	CH_3OH/NaOH	24	0
Cu^{II} acetate	CH_3OH	04	50(2)[b]
No catalyst	CH_3OH/NaOH	24	0

Reaction conditions: 2,6-DTBP (1 mmol), catalyst (1 mol%) and NaOH (10 mol%), under air, 25 °C.
[a] Isolated yield.
[b] Without NaOH.

complexes [188,193–202] as catalysts but use of iron and manganese are relatively less [76,187,203]. Organic ligands have also been found to be effective catalyst to form DPQ as major product [204]. It was also found that hydrogen peroxide in presence of iodine leads to selective formation of BQ [205].

The catalytic oxidation of 2,6-DTBP was performed by us by dissolving 2,6-DTBP in methanol followed by addition of 10 mol% sodium hydroxide in water and 1 mol% M^{II}-acetate was then added to it. Reaction mixture was stirred for 4–24 h at 25 °C. As the reaction progressed DPQ was visibly witnessed as a reddish brown precipitate, which was finally collected by filtration and dried and analyzed for purity by ESI–MS and NMR spectroscopy (Figs. S20–S21). Among the six M^{II} acetates used, only Mn^{II}, Co^{II}, Cu^{II} were found to be active (Table 4). Cu^{II} acetate showed a noted exception; it did not require the addition of base, it was active without any base being added and the yield did not change much even after addition of the optimized 10 mol% NaOH. Based on the literature evidences suggesting the deprotonation of OH is the first step [190,206] it seems Cu due to its higher Lewis acidic nature is able to deprotonate the phenolic OH through interaction with the phenol oxygen.

4. Conclusions

The studies of CO and PHS activity using the metal acetates showed that Mn is the most active metal ion and the substrate may act as ligand to form the active catalytic species. It seems that the active species responsible for the oxidation of CO are the bis or tris–catechol bound metal–catecholate complexes formed during the reaction. This is also supported by our earlier work on Mn^{III} acetate [32], where we could find binding of three DTBC. Earlier works with substituted catechols as ligand using Mn, Co, Fe and Cu as metal ions also support the formation of similar species [152–155,207–210]. It seems that Mn is the best choice as the metal and it needs to be more explored with suitable ligands for tuning the activity. Mn-acetate shows the involvement of hydroxyl radical whereas the Co^{II} and Fe^{II} show involvement of both peroxo and hydroxyl radical. In contrast although the well established mechanistic pathway of the enzyme shows no involvement of hydrogen peroxide but clearly, Cu^{II}, the native metal for CO and PHS, oxidizes DTBC by generation of hydrogen peroxide. Hence, the influence of the protein donors in changing the mechanistic pathway of a metal ion also seems evident. Furthermore, Mn also appears to be the best metal of choice among the 3d-transition metals for conversion of 2-aminophenol to 2-aminophenoxazinone. In addition Mn is also most active for oxidative coupling of 2,6-di-*tert*-butylphenol (2,6-DTBP). However, the presence of Cu^{II} as catalyst does not require the presence of base. The above coupling reaction also hints towards nature choice of Cu^{II} for the CO and PHS proteins, since apart from the geometrical constraints, nature may be exploiting the Lewis acidic property of Cu to bind and activate the respective substrates.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2015.06.020

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