

Bioinspired Benzene Hydroxylation by Non-Heme Model Systems

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by
K. Anandababu M.Sc.,
(Regn. No: F8833)



Department of Physical Chemistry
School of Chemistry
Madurai Kamaraj University
(*University with Potential for Excellence*)
Madurai – 625 021
India.

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Chapter I. Introduction

Phenol is one of the valuable chemical intermediates for the synthesis of various industrial products such as phenol-formaldehyde resins, bisphenol A, caprolactam etc.¹⁻⁴ Phenol and its derivatives are important precursor an industries of dyes, pharmaceuticals, medicines, etc.⁵ Industrially phenol produced by cumene process (three-step process), in which propylation of benzene forms cumene, which undergoes autoxidation forms cumene hydrogen peroxide (CHP) *via* cumene peroxide radical. The CHP under Hock rearrangement to produce phenol (yield~ 5%) and acetone as a by-product. Drawbacks of the above method are, three-step process, CHP is hazardous, high energy consumption and by-products like acetone formed.⁵ And also other techniques used to phenol from benzene are Sulfonation, Chlorination, cyclohexanone process, benzoic acid process.^{4b,c} To overcome above drawbacks, the researchers focused a much simpler means single-step reaction and more efficient process that proceeds under mild conditions is desired, which can preferably overcome the disadvantages of the above process. Then exploring the catalytic chemistry using metal complexes as a catalyst like homogeneous, heterogeneous, photocatalyst and electrochemically. An economically and environmentally benign oxidant such as O₂,^{6a} H₂O₂,^{6b} N₂O,^{6c} air/CO^{6d} has remained a focal point for extensive research efforts. In this process, one of the C–H bonds is activated and then hydroxylated. However, the high bond energy (460 kJ mol⁻¹) makes it impossible without the help of a catalyst.

The heterogeneous catalysts such as TS-1,^{6a, 7a} SBA-15,^{7b,c} other molecular sieves,^{7d} hydrotalcites,^{7e} MWCNTs,^{7f} heteropolyacids^{7g} loaded with metal ions have shown high efficiencies. However, leaching of active species hinders their further application at an industrial scale and it is not clarified by mechanistically due to the spectroscopic observation of solid surface is very difficult. Homogeneous catalysts possess a number of advantages, for example, they can operate under mild conditions and the catalytic performance is tuneable through ligand design and appropriately selecting a metal ion, catalytic performance could be further improved and depend on

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metal oxidation state mechanism was easy to propose.⁸ However, to date, only limited reports have been devoted to developing homogeneous catalysts.⁹ The most challenging thing is oxidation aromatic compounds, naturally, heme and non-heme iron enzymes play a big role in this conversions.^{10a-d} Recently the study of chemical models that mimic oxygenase has developed.^{10e-f} Many bioinspired catalyst systems are used hydroxylation reaction are cytochrome P450,^{11a} Xanthine oxidase,^{11b} dopamine β -hydroxylase,^{11c} phenylalanine hydroxylase,^{11d} methane monooxygenase.^{11e} Recently non-heme models are used as a catalyst for hydroxylation of alkenes and aromatics.¹² Few transition metal complexes were employed as the catalysts (V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ru) for C-H activation.^{8,13}

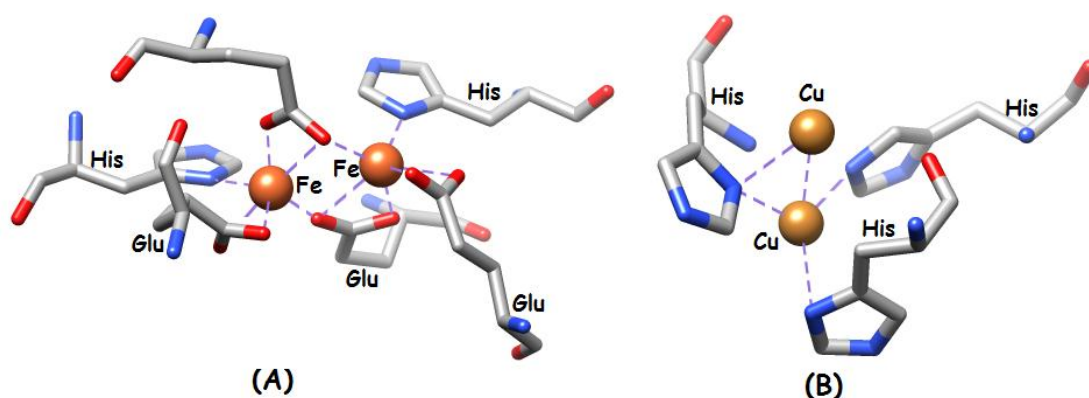
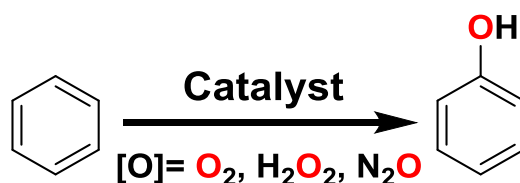


Figure. 1 Active site soluble Methane Monooxygenase (A), particulate Methane Monooxygenase (B).



Activation of the benzene C-H bond has not yet been fully investigated from a mechanistic viewpoint. The C-H activation by enzyme using molecular O₂ passes through several metal-oxygen intermediates, some of the intermediates is answerable for the substrate oxidation reaction.¹¹ From the recommendations of enzyme catalytic cycle, we focused to develop a catalyst for selective oxidation of C-H bond reaction¹⁸ and the reactive species that catalyzes the direct benzene hydroxylation over heterogeneous catalysts.¹⁰ The unknown reactive species have been carried out via kinetic studies, intricate reaction mechanisms are often needed to account for the

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reactivity. We planned to synthesize and characterize bioinspired catalyst using Fe, Co, Ni and Cu, which are known in biological oxidation and most abundant and exceptional candidate for benzene hydroxylation reaction.

Reference

1. Fiege, H.; Voges, H. W.; Hamamoto, T.; Umemura, S.; Iwata, T.; Miki, H.; Fujita, Y.; Buysch, H. J.; Garbe, D.; Paulus, W. Ullmann's Encyclopedia of Industrial Chemistry; Wiley-VCH: Weinheim, Germany, **2000**; Vol. 26 (phenol derivatives), pp 521-576.
2. Borah, P.; Ma, X.; Nguyen, K. T.; Zhao, Y. *Angew. Chem. Int. Ed.*, **2012**, *51*, 7756–7761.
3. Khatri, P. K.; Singh, B.; Jain, S. L.; Sain, B.; Sinha, A. K. *Chem. Commun.*, **2011**, *47*, 1610–1612.
4. Weber, M.; Kleine-Boymann, M. Ullmann's Encyclopedia of Industrial Chemistry, **2004**. b) Panov, G. I.; Uriarte, A. K.; Rodkin, M. A.; Sobolev, V. I., **1988**, *Catal. Today*, *41*, 365. c) Panov, G. I., *Cattech.*, **2000**, *41*, 18.
5. Weber, M.; Weber, M.; Kleine-Boymann, M. In Ullmann's Encyclopedia of Industrial Chemistry; Wiley-VCH: Weinheim, Germany, **2000**. b) Weissermel, K.; Arpe, H. J. *Industrial Organic Chemistry*, John Wiley & Sons, 3rd edn, **2008**. c) Schmidt, R. J. *Appl. Catal., A*, **2005**, *280*, 89-103
6. (a) Shibata, Y.; Hamada, R.; Ueda, T.; Ichihashi, Y.; Nishiyama, S.; Tsuruya, S. *Ind. Eng. Chem. Res.*, **2005**, *44*, 8765-8772. (b) Tanev, P. T.; Chibwe, M.; Pinnavaia, T. J. *Nature*, **1994**, *368*, 321- 323. c) Xin, H.; Koekkoek, A.; Yang, Q.; van Santen, R. A.; Li, C.; Hensen, E. J. M. *Chem. Commun.*, **2009**, 7590-7592. (d) Acharyya, S. S.; Ghosh, S.; Bal, R. *ACS Appl. Mater. Interfaces*, **2014**, *6*, 14451-14459.
7. a) Bianchi, D.; Balducci, L.; Bortolo, R.; D'Aloisio, R.; Ricci, M.; Spano, G.; Tassinari, R.; Tonini, C.; Ungarelli, R. *Adv. Synth. Catal.*, **2007**, *349*, 979–986. b) Kalbasi, R. J.; Massah, A. R.; Zamani, F.; Bain, A. D.; Berno, B., *J. Porous Mater.*, **2011**, *18*, 475–482. c) Kharat, A. N.; Moosavikia, S.; Jahromi, B. T.; Badiei, A. *J. Mol. Catal. A: Chem.*, **2011**, *348*, 14–19. d) Qi, X. Y.; Li, J. Y.; Ji, T. H.; Wang, Y. J.; Feng, L. L.; Zhu, Y. L.; Fan, X. T.; Zhang, C. *Microporous Mesoporous Mater.*, **2009**, *122*, 36–41. e) Dubey, A.; Kannan, S. *Catal. Commun.*, **2005**, *6*, 394–398. f) Song, S. Q.; Yang, H. X.; Rao, R. C.; Liu, H. D.; Zhang, A. M. *Appl. Catal., A*, **2010**, *375*, 265–271. g) C. H. Lee, T. S. Lin, and C. Y. Mou, *J. Phys. Chem. B*, **2003**, *107*, 2543–2551.
8. a) Conde, A.; Diaz-Requejo, M. M.; Perez, P. J. *Chem. Commun.*, **2011**, *47*, 8154–8156. b) Itoh, S.; Tachi, Y. *Dalton Trans.* **2006**, 4531–4538. (b) Nagataki, T.; Ishii, K.; Tachi, Y.; Itoh, S. *Dalton Trans.* **2007**, 1120–1128.
9. a) Carneiro, L.; Silva, A. R., *Catal. Sci. Technol.*, **2016**, *6*, 8166–8176. b) T suji, T.; Zaoputra, A. A.; Hitomi, Y.; Mieda, K.; Ogura, T.; Shiota, Y.; Yoshizawa, K.; Sato, H.; Kodera, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 7779–7782.
10. a) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L., *Chem. Rev.*, **2004**, *104*, 939-986. (b) Meunier, B.; de Visser, S. P.; Shaik, S. *Chem. Rev.*, **2004**, *104*, 3947-3980. (c) Abu-Omar, M. M.; Loaiza, A.; Hontzeas, N. *Chem. Rev.*, **2005**, *105*, 2227-2252. (d) Bruijninx, P. C. A.; van Koten, G.; Klein Gebbink, R. J.

Synopsis

- M. *Chem. Soc. Rev.*, **2008**, *37*, 2716-2744. e) Akhrem, A. A.; Metelitsa, D. I.; Skurko, M. E., *Russ. Chem. Rev.*, *1975*, *44*, 398. f) Ullrich, V. *Angew. Chem. Int. Ed.*, **1972**, *84*, 701.
11. a) Groves, J. T.; McClusky, G. A.; White, R. E.; Coon, M. J., *Biochem. Biophys. Res. Commun.*, **1978**, *81*, 154. b) Que Jr., L. *Acc. Chem. Res.*, **2007**, *40*, 493–500. c) Bray, R. C.; Palmer, G.; Beinert, H. (T. King, H. S. Mason, and M. Morrison, eds.), Vol. 1, p. 359. Wiley, New York, **1965**. d) Kaufman, S., *Adv. Chem. Series*, **1968**, *77*, 172. e) Kaufman, S.; Fisher, D. B. in "Molecular Mechanisms of Oxygen Activation" (O. Hayaishi, ed.), p. 285. Academic Press, New York, **1974**. f) Wang, V. C.-C.; Maji, S.; Chen, P. P.-Y.; Lee H. K.; Yu, S. S.-F.; Chan, S. I., *Chem. Rev.*, **2017**, *117*, 138574-8621.
12. a) Mekmouche, Y.; Menage, S.; Toia-Duboc, C.; Fontecave, M.; Galey, J.-B.; Lebrun, C.; Pecaut, J. *Angew. Chem. Int. Ed.*, **2001**, *40*, 949–952. b) Costas, M.; Mehn, M. P.; Jensen, M.P.; Que, L. *Chem. Rev.*, **2004**, *104*, 939–986.
13. a) Bianchi, D.; Bortolo, R.; Tassinari, R.; Ricci, M.; Vignola, R. *Angew. Chem. Int. Ed.*, **2000**, *39*, 4321-4323; b) Mori, K.; Kagohara, K.; Yamashita, H. *J. Phys. Chem. C* **2008**, *112*, 2593-2600; c) Roy, P.; Dhara, K.; Manassero, M.; Banerjee, P. *Eur. J. Inorg. Chem.* **2008**, 4404-4412; d) Bartoli, J. F.; Mouries-Mansuy, V.; Le Barch-Ozette, K.; Palacio, M.; Battioni, P.; Mansuy, D. *Chem. Commun.*, **2000**, 827-828; f) Wang, X.; Wu, J.; Zhao, M.; Lv, Y.; Li, G.; Hu, C. *J. Phys. Chem. C* **2009**, *113*, 14270-14278; g) Shulpin, G. B.; Kozlov, Y. N.; Shul'pina, L. S.; Carvalho, W. A.; Mandelli, D. *RSC Adv.* **2013**, *3*, 15065-15074; h) Wienhöfer, G.; Schröder, K.; Möller, K.; Junge, K. M. Beller, *Adv. Synth. Catal.* **2010**, *352*, 1615-1620.
14. Kovaleva, E.G.; Lipscomb, J.D., *Nat. Chem. Biol.*, **2008**, *4*, 186.

Chapter II. Materials and Methods

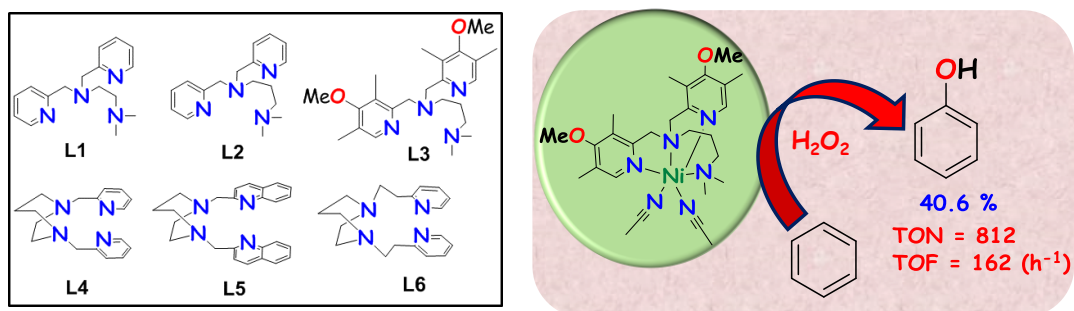
In this chapter, materials, synthesis of ligands *N,N*-Bis(2-pyridylmethyl)-*N',N'*-dimethylethane-1,2-diamine (L1), *N,N*-bis(2-pyridylmethyl)-*N',N'*-dimethyl propane-1,3-diamine (L2) have been synthesized by reductive amination reaction.^{18a} The synthesis of *N¹,N¹*-bis((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-*N³,N³*-dimethyl propane-1,3-diamine (L3), 1,4-bis[(pyridin-2-yl-methyl)]-1,4-diazepane (L4) and 4-bis[2-(quinoline-2-yl)-methyl]-1,4-diazepane (L5), 1,4-bis[2-(pyridin-2-yl)ethyl]-1,4-diazepane (L6), 1,1,2-tri(pyridin-2-yl)propan-1-ol and complex prepared from corresponding metal precursors characterization, spectral techniques and DFT software used to optimization will be presented.

Chapter III. Highly Efficient Nickel(II) Complexes of N₄-Ligands for Selective Hydroxylation of Benzene

In this chapter, we report the synthesis and characterization of nickel(II) complexes of N₄ ligands as the efficient catalysts for selective benzene hydroxylation using H₂O₂ at 60 °C and 25 °C. The present ligand architectures and their higher Ni²⁺ → Ni³⁺ oxidation potential provides significant differences from those previously reported catalysts and thus improved catalytic performance. Previously Y. Morimoto et al used Nickel(II) TEPA (tris[2-(pyridine-2-yl)ethyl]amine) metal complex used as a catalyst for benzene hydroxylation and produce 21% of phenol with TON of 749 using H₂O₂ as oxidant at 60°C.² The nickel(II) complexes of N₄-ligands have been synthesized and characterized by ESI-MS and elemental analysis. The above complexes are efficient and selective catalysts for hydroxylation of benzene using H₂O₂. These complexes exhibited Ni²⁺/Ni³⁺ redox couples around 0.892 - 0.957 V vs Ag/Ag⁺ in acetonitrile. Out of the six complex **2** has been structurally characterized and adopted an octahedral geometry. The highest yield of phenol achieved using benzene (0.45 mL, 5 mmol), catalytic amount of complexes **1-6** (2.5 μmol, 0.05 mol%) were dissolved in acetonitrile (3.0 mL), triethylamine (5.0 μmol), and 30% of aqueous H₂O₂ (25 mmol) were added very slowly into the reaction mixture under constant stirring at 60 °C and stirring was continued for 5 hours produced phenol exclusively with excellent yields 15.9-40.6%. while the same reaction is done at 25°C, the yield of phenol was reduced but the selectivity raised up to 98.1%. This is unprecedented highest catalytic efficiency achieved to date for benzene hydroxylation using 0.05 mol% catalyst and only five equivalents of H₂O₂. The over oxidation of phenol was carefully avoided by using a lower amount of H₂O₂ and slower addition, whereas an excess of H₂O₂ was utilized in the previous reports. The complexes of tripodal ligands (**1-3**) showed the highest catalytic efficiency than cyclic diazepane backbone (**4-6**), which is possibly influenced by steric, electronic complexes.³ KIE of complex **1 – 6** determined shows 0.98 – 1.05, isotope labeling experiment show, ¹⁸O was incorporated into phenol product nearly quantitatively (92.46%). The proposed key intermediate bis(μ-oxo)dinickel(III) species were characterized by spectral methods and its geometry was optimized by DFT calculations. To our best knowledge, our report is the novel example of Ni(II)-N₄ catalysts for benzene

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hydroxylation, which showed selective phenol formation up to 40.6% yield, TON, 812 and turnover frequency (TOF) up to 162 h⁻¹ using relatively lower catalyst loading (0.05 mol%) and five equivalents of H₂O₂ at 60 °C. Interestingly, 21.4% of phenol production was achieved at 25 °C with TON of 424 under identical conditions. They are the highest yields and catalytic efficiency reported so far in the literature.



Reference

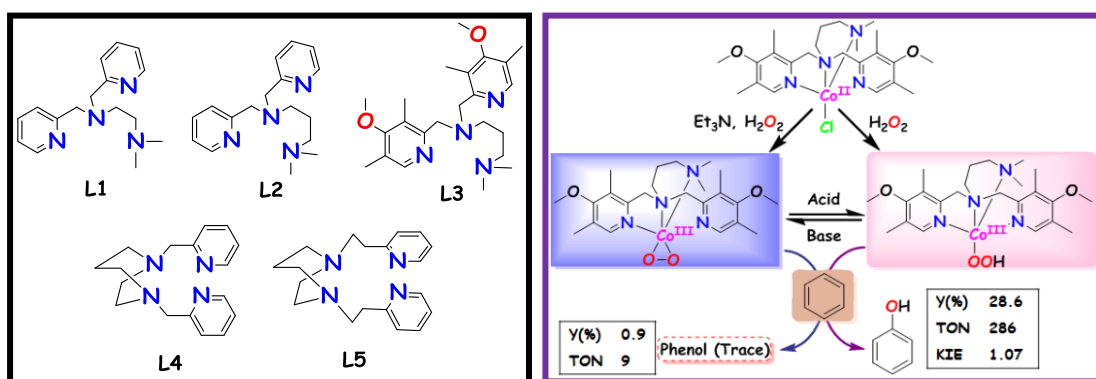
1. a) Bianchi, D.; Bortolo, R.; Tassinari, R.; Ricci, M.; Vignola, R. *Angew. Chem. Int. Ed.*, **2000**, *39*, 4321-4323; b) Mori, K.; Kagohara, K.; Yamashita, H. *J. Phys. Chem. C* **2008**, *112*, 2593-2600; c) Roy, P.; Dhara, K.; Manassero, M.; Banerjee, P. *Eur. J. Inorg. Chem.* **2008**, 4404-4412; d) Bartoli, J. F.; Mouries-Mansuy, V.; Le Barch-Ozette, K.; Palacio, M.; Battioni, P.; Mansuy, D. *Chem. Commun.*, **2000**, 827-828; f) Raja, R.; Thomas, J. M.; Dreyer, V. *Catal. Lett.* **2006**, *110*, 179-183; g) Wang, X.; Wu, J.; Zhao, M.; Lv, Y.; Li, G.; Hu, C. *J. Phys. Chem. C* **2009**, *113*, 14270-14278; h) Shul'pin, G. B.; Kozlov, Y. N.; Shul'pina, L. S.; Carvalho, W. A.; Mandelli, D. *RSC Adv.* **2013**, *3*, 15065-15074; i) Wienhöfer, G.; Schröder, K.; Möller, K.; Junge, K. M. Beller, *Adv. Synth. Catal.* **2010**, *352*, 1615-1620.
2. Morimoto, Y.; Bunno, S.; Fujieda, N.; Sugimoto, H.; Itoh, S., *J. Am. Chem. Soc.*, **2015**, *137*, 5867-5870.
3. a) Itoh, S.; Tachi, Y. *Dalton Trans.* **2006**, 4531-4538. (b) Nagataki, T.; Ishii, K.; Tachi, Y.; Itoh, S. *Dalton Trans.* **2007**, 1120-1128.

Chapter IV. One-Step Benzene Hydroxylation Triggered by Co(III)-Peroxo Intermediate

The cobalt(II) complexes of tetradentate ligands (N₄) have been synthesized and characterized as the catalysts for one-step phenol formation from benzene. Among the five four complex structure has analyzed by single-crystal XRD. The molecular structure of complexes showed distorted trigonal bipyramidal geometry (τ , 0.49 – 0.88) with Co-N_{amine} (2.104 – 2.254 Å) and Co-N_{Py} bond distances (2.043 – 2.099 Å). The complexes exhibited Co²⁺/Co³⁺ redox potential around 0.489 - 0.512 V

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in acetonitrile. They catalyzed selective benzene hydroxylation using H₂O₂ (30%) and afforded phenol as the major product. Reaction condition is benzene (0.45 mL, 5 mmol), a catalytic amount of complexes **1-5** were dissolved in acetonitrile and 30% of aqueous H₂O₂ were added very slowly into the reaction mixture under constant stirring at 60 °C and stirring was continued for 5 hours produced phenol exclusively with excellent yields 18.1-28.6%. The maximum yield up to 28.6% was observed with turnover number (TON) of 286 at 60°C and 19.1% and TON of 191 at 25°C, which are the highest catalytic performances achieved to date using cobalt(II) complexes as catalysts. This aromatic hydroxylation presumably proceeded *via* cobalt(III)-peroxo species are sideon-Co(III)-peroxo and Co(III)-hydroperoxo, which was characterized by spectral and DFT methods. Sideon-Co(III) species facile deformylation of 2-phenylpropionaldehyde,² endon Co(III) species corresponds for OAT type of reaction like benzene hydroxylation reaction.³ Reactivity of substituted benzene is correlated with Hammett constants, which shows electron-donating groups such as -Me and -OMe showed better hydroxylation as compared to the electron-withdrawing group (-Cl, -NO₂). KIE values were calculated from GC-MS as 0.98 -1.07 for **1 – 5**. 89% of ¹⁸O incorporated into phenol was observed using H₂ ¹⁸O₂. Proposed intermediate was optimized DFT and TDDFT calculations show the energy of optimized structure and compare with experimental spectrum.



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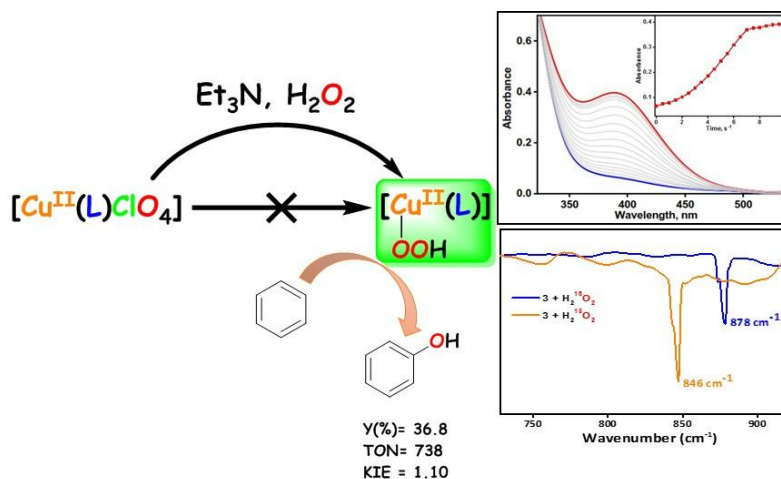
1. a) McDonald, A. R.; Que, L. Jr., *Coord. Chem. Rev.*, **2013**, 257, 414-428. b) Que, L. Jr., *Acc. Chem. Res.*, **2007**, 40, 493-500.
2. a) Cho, J.; Sarangi, R.; Kang, H. Y.; Lee, J. Y.; Kubo, M.; Ogura, T.; Solomon, E. I.; Nam, W. *J. Am. Chem. Soc.*, **2010**, 132, 16977–16986. b) Zhang, Q.; Taylor, A. B.; Bronston, F. M.; Gordon, J. D.; Goldsmith, C. R. *Inorg. Chem.* **2017**, 56, 773-782.

3. a) Tcho, W. -Y.; Wang, B.; Lee, Y. -M.; Cho, K. -B.; Shearer, J.; Nam, W. *Dalton Trans.*, **2016**, *45*, 14511–14515. b) Wang, C.-C.; Chang, H.-C.; Lai, Y.-C.; Fang, H.; Li, C.-C.; Hsu, H.-K.; Li, Z.-Y.; Lin, T.-S.; Kuo, T.-S.; Neese, F.; Ye, S.; Chiang, Y.-W.; Tsai, M.-L.; Liaw, W.-F.; Lee, W.-Z. *J. Am. Chem. Soc.*, **2016**, *138*, 14186-14189. c) Kim, D; Cho, J.; Lee, Y.-M.; Sarangi, R.; Nam, W. *Chem. Eur. J.*, **2013**, *19*, 14112 – 14118.

Chapter V. Bioinspired Copper(II) Complexes N₄ Ligands as Catalysts for Benzene Hydroxylation

Copper complexes of active-oxygen species, such as superoxide (O₂), hydroperoxide (HOO), alkyl- or acylperoxide (ROO), and oxide (O₂) have been invoked as key reactive intermediates in a wide variety of redox reactions involved not only in biological systems but also in numerous catalytic oxidation processes.¹ Direct hydroxylation of benzene to phenol is important for the synthesis of various organic compounds and the economic point of view. The copper(II) complexes of N₄-ligands have been synthesized and characterized as the efficient catalysts for the hydroxylation of benzene using H₂O₂ as oxidant. All the complexes exhibited Cu²⁺ → Cu⁺ reduction potential -0.352 to -0.618 V vs Ag/Ag⁺ in acetonitrile. The molecular structure of **2** exhibits distorted trigonal bipyramidal (τ , 0.70) and **4** exhibits the square pyramidal geometry (τ , 0.037). The complexes catalyzed direct benzene hydroxylation using H₂O₂ as an oxygen source and afforded phenol exclusively with excellent yields up to 36.8% and turnover number (TON) of 738. This is the highest catalytic efficiency achieved to date for benzene hydroxylation using. The kinetic isotope effect (KIE) values (0.94 - 1.10) are suggesting that the involvement of Copper-bound oxygen species as a key intermediate. The benzene hydroxylation reaction possibly proceeds via key intermediate Cu^{II}-OOH species, which was characterized by ESI-MS, vibrational and electronic spectral methods. The formation constant of key intermediates was calculated as 1.1 - 2.9 × 10⁻² s⁻¹ by following the appearance of O (π^*_σ) → Cu LMCT transition around 375 nm. The Cu^{II}-OOH intermediate was characterized by spectral methods and its geometry was optimized by DFT calculation. The isotope-labeling experiments using H₂¹⁸O₂ showed 92.46% incorporation of ¹⁸O, reveals that H₂O₂ is the key oxygen supplier to form phenol. The catalytic efficiencies of complexes are strongly influenced by geometrical configuration, fine-tuned by ligand architecture.

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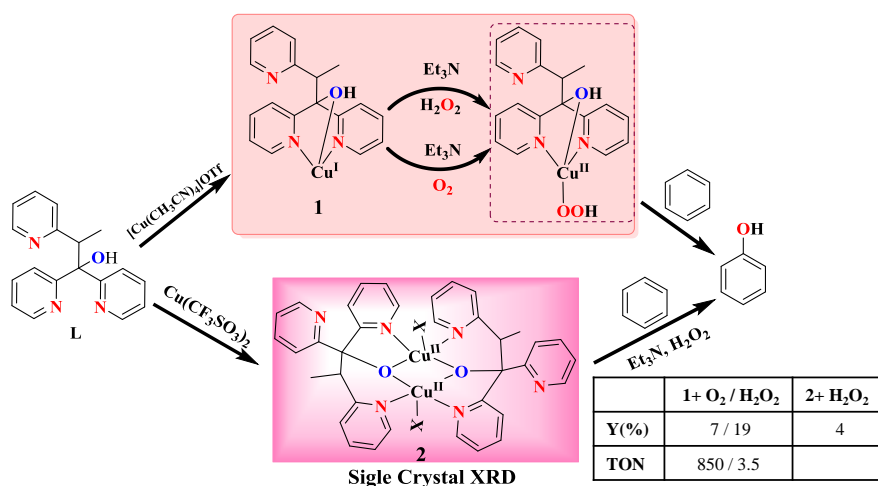
1. a) Kitajima, N.; Moro-oka, Y. *Chem. Rev.*, **1994**, *94*, 737–757. b) Klinman, J. P. *Chem. Rev.*, **1996**, *96*, 2541–2562. c) Itoh, S., *Curr. Opin. Chem. Biol.*, **2006**, *10*, 115–122. d) Punniyamurthy, T.; Rout, L. *Coord., Chem. Rev.*, **2008**, *252*, 134–154. d) Himes, R. A.; Karlin, K. D. *Curr. Opin. Chem. Biol.*, **2009**, *13*, 119–131.

Chapter VI. Aromatic Hydroxylation by Copper(I) complex: A Relevant Functional Model for Copper Monooxygenase Enzymes

Metalloenzymes play an important role in biology to generate metal-oxo species, which reacts with the various substrate to give the desired product.¹ In particularly non-heme copper monooxygenase enzymes like dopamine β -monooxygenase (D β M), methane monooxygenase (MMO), tyrosinase (Ty) are facile oxygenase/oxidation reactions.² Especially dicopper active sites are known to catalyze oxygenation/oxidation various aliphatic and aromatic substrates.³ Chiral based 1,1,2-tri(pyridin-2-yl)propan-1-ol as a ligand, $[\text{Cu}^{\text{I}}(\text{L})]^+\text{CF}_3\text{SO}_3$ **1** complex has been synthesized and probed as functional models for copper monooxygenase enzymes. Further, **1** on crystallization in the open air in CH_3CN results in paddlewheel complex of **3** with two copper centers in a mixed oxidation state $\text{Cu}^{\text{I}}\text{-Cu}^{\text{II}}$ $[\text{Cu}_2\text{L}_2](\text{SO}_3\text{CF}_3)_2\cdot\text{H}_2\text{O}$ with Cu-Cu distance of 2.96 Å. This is further characterized by ESI-MS, EPR, and single-crystal XRD analysis. Individually, $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ with ligand yields **2** has dicopper centers similar to **3** with $\text{Cu}^{\text{II}}\text{-Cu}^{\text{II}}$ distance of 2.97 Å with H_2O in the outside coordination sphere. Thus, this Cu-Cu shorter distance of < 3.0 Å is speculated as playing a vital role in C-H activation through the formation of (Cu_2O_2) species. The complex **1** with H_2O_2 selectively functionalized the C-H of benzene to phenol affording 19% yield with TON of 70 at 60°C. Endurance test of the

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catalyst **1** showed phenol conversion with TON 850 after 120 hours at 60°C, evident that **1** being a good catalyst of selective aromatic hydroxylation. Electronic spectra of **1** at 25°C with O₂ and H₂O₂ both showed a steep increase at 360 and 650 nm reveals that key intermediate being Cu^{II}-OOH species formation. Further infrared spectra signature at 890 cm⁻¹ inevitably supports the existence of Cu^{II}-OOH species formation during catalysis. Isotopic studies for the benzene hydroxylation of **1** with using H₂¹⁸O₂ and H₂O₂ in presences of H₂¹⁸O shows 95.3% and >3% ¹⁸O labeled phenol respectively. KIE studies with C₆H₆/C₆D₆ (1:1) in H₂O₂ results in *k_H*/*k_D* being 1.03. NIH shift experiment using **1** with C₆H₅D showed the complete formation of phenol without NIH shift (a shift of the deuterium on the attacked carbon to the neighboring carbon). Thus by overall spectroscopic evidence, the mechanism of benzene hydroxylation is discussed.



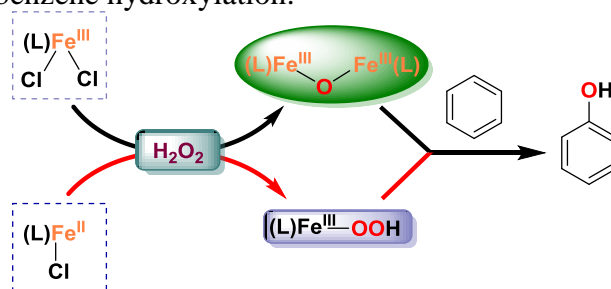
Reference

1. a) A. R. McDonald, L. Que, Jr., *Coord. Chem. Rev.*, **2013**, 257, 414-428. b) L. Que, Jr., *Acc. Chem. Res.*, **2007**, 40, 493-500.
2. a) Bray, R. C.; Palmer, G.; Beinert, H. (T. King, H. S. Mason, and M. Morrison, eds.), Vol. 1, p. 359. Wiley, New York, **1965**. b) Kaufman, S.; Fisher, D. B. in "Molecular Mechanisms of Oxygen Activation" (O. Hayaishi, ed.), p. 285. Academic Press, New York, **1974**.
3. T suji, T.; Zaoputra, A. A.; Hitomi, Y.; Mieda, K.; Ogura, T.; Shiota, Y.; Yoshizawa, K.; Sato, H.; Kodera, M. *Angew. Chem. Int. Ed.* **2017**, 56, 7779–7782.

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Chapter VII. Non-Heme Iron(II/III) Complexes as Catalysts for Aromatic C-H Activation

Iron is a most abundant metal in the earth crust and also play a role in biological systems. Non-heme iron enzymes such as methane monooxygenases (MMO) and cytochromes P450 and p-toluene monooxygenase (T4MO) have been studied as a catalyst for oxidation of hydrocarbons. They generate the distinct oxidizing intermediate on reaction with oxygen, which is transfer to the substrate for C-H activation. The bioinspired complexes are capable of mimicking the catalytic (and in some cases the structural) features of these enzymes, which is a matter of high current interest to date.¹ The ligands with N4 donor are known to display biomimetic oxidation catalysis. The iron(II/III) complexes ($[\text{Fe}(\text{L})\text{Cl}]\text{BPh}_4$ **1a** - **5a**; $[\text{Fe}(\text{L})\text{Cl}_2]\text{BPh}_4$, **1b** - **5b**) of ligands L1 - L5 were synthesized and characterized. The complex $[\text{Fe}(\text{L4})\text{Cl}]\text{BPh}_4$ **3a** was crystallized and determined the structure by single-crystal X-ray technique, which showed distorted square pyramidal geometry ($\tau = 0.17$). All the iron(II/III) complexes were used as catalysts for benzene hydroxylation using 0.01 mmol of catalyst, 10 mmol of H_2O_2 as an oxidant slowly added, 5 mmol of benzene at $60^\circ\text{C}/25^\circ\text{C}$. They showed the formation of phenol up to yield 10.4-20.8% at 60°C with the selectivity of 38-59.9%. Under identical reaction condition using of iron(III) complex as a catalyst, phenol yield was slightly enhanced (12.4 - 23.8%). The isotopic labeling studies show 89.6% of ^{18}O incorporated phenol forms using $\text{H}_2^{18}\text{O}_2$. KIE value (0.95-1.00) shows there is no radical or Fenton type reaction. After addition of H_2O_2 to iron(II) complex (**2a**, **3a**) shown new green species with formation electronic transitions at 500 nm (**2a**), 454, 495, 546 nm (**3a**) at -40°C , which may be corresponding to $\text{Fe}^{\text{III}}\text{OOH}$ species. It was also confirmed by ESI-MS, (m/z): 373 (2a), 489 (3a). Addition of H_2O_2 to iron(III) complexes showed a new absorption band around 350-360 nm, which may correspond to $\text{Fe}^{\text{III}}(\mu\text{-O})\text{Fe}^{\text{III}}$ and is responsible for benzene hydroxylation.



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Reference

1. a) Nam, W.; McCleverty, J. A.; Meyer, T. J. (Eds. in chief); Que Jr., L.; Tolman W. B. (Eds.), *Comprehensive Coordination Chemistry II*, Elsevier, **2004**, 8, 281–307. b) Frausto da Silva, J. J. R.; Williams, R. J. P., *The Biological Chemistry of the Elements the Inorganic Chemistry of Life*, second ed., Oxford University Press, Oxford, **2001**; c) Lippard, S. J.; Berg, J. M., *Principles of Bioinorganic Chemistry*, University Science Books, Mill Valley, **1994**; d) Kaim, W.; Schwederski, B., *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*, John Wiley & Sons, Chichester, **1994**.
2. a) Fontecave, M; Roy, B.; Lambeaux, C., *J. Chem. Soc. Chem. Commun.*, **1991**, 939. b) Lyakin, O. Y.; Zima, A. M.; Tkachenko, N. V.; Bryliakov, K. P.; Talsi, E. P., *ACS Catal.*, **2018**, 8, 5255-5260.