Steric effects in the design of Co-Schiff base complexes for the catalytic oxidation of lignin models to para-benzoquinones†

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New Co-Schiff base complexes that incorporate a sterically hindered ligand and an intramolecular bulky piperazine base in close proximity to the Co center are synthesized. Their utility as catalysts for the oxidation of para-substituted lignin model phenols with molecular oxygen is examined. Syringyl and guaiacyl alcohol, as models of S and G units in lignin, are oxidized in good yield using a catalyst bearing an N-benzylpiperazinyl substituent, with the catalysts displaying improved reactivity for G oxidation. Computational evaluation of the catalysts shows that the piperazinyl substituent is within bonding distance of the Co center. The increased steric interference is suggested as the source of increased G reactivity.

Introduction

By using renewable carbon (biomass) as a raw material, the integrated biorefinery is emerging as an alternative to the petrochemical refinery for the simultaneous production of bio-based chemicals and fuels. Central to the viability of this new industry will be its capacity to transform each of the primary components of biomass into biobased products.1 Lignin offers both opportunity and challenge in this regard, as it can be nearly 25% of lignocellulosic biomass, making it the second most abundant source of renewable carbon in the biosphere, and the most likely source of biobased aromatics.2 However, lignin possesses a highly heterogeneous polyaromatic structure. Heterogeneity is introduced during a biosynthetic process that couples delocalized phenoxyl radicals formed from a small group of primary monolignols (Fig. 1), leading to a variety of different substructural units.3 Lignin from woody feedstocks is constructed mostly from syringyl (S) and guaiacyl (G) units derived from sinapyl and coniferyl alcohol, respectively. Herbaceous feedstocks (grasses) incorporate p-hydroxyphenyl (H) units into the lignin polymer as well as coumaric and ferulic acid as end caps and crosslinkers.4 Moreover, the structure of lignin as found in nature changes, often dramatically, during processes used for its isolation within the biorefinery.5 Effective use of lignin therefore requires processes able to accommodate all of the various substructural units present within the raw material.

The electron rich nature of the aromatic units in lignin suggests that they should be subject to selective oxidation. Indeed, the pulp and paper industry practices nonselective oxidation of lignin on a massive scale for the purposes of lignin removal from cellulose pulp.6 Recent reports describe new oxidative methodology for transforming lignin models into low molecular weight aromatics using reductive processes catalyzed by Ru,7 Ni8 and Pd,9 oxidative and non-oxidative processes catalyzed by Co10 and V,11 or organocatalytic processes using TEMPO.12 These studies focus almost exclusively on the cleavage of dimeric, non-phenolic b-aryl ether models, representative of lignin’s b-O-4 linkage, which can account for 50–65% of the substructural units present in native lignin. Unfortunately, a focus on this linkage may not provide an appropriate representation of the lignin actually available for...
conversion within the biorefinery because leading processes for biomass separation may eliminate β-O-4 units during lignin isolation. Moreover, as these β-O-4 units are lost, there is a concomitant increase in free phenolic hydroxyl functionality. Thus, catalytic processes targeting conversion of lignin-like phenols would provide a more realistic probe of lignin as a chemical feedstock.

Co-Schiff base complexes catalyze the aerobic oxidation of phenols under mild conditions (Fig. 2). In the presence of an external ligand such as pyridine, the Co catalysts [e.g., Co(salen), 1] bind molecular oxygen to form a Co-superoxo complex 2. With simple Co-Schiff base complexes, formation of 2 is significantly improved by addition of pyridine as an external axial ligand because 1 itself binds oxygen poorly. The resulting complex 2 abstracts a phenolic hydrogen from the substrate to generate phenoxy radical 3, initiating a process that affords production of para-benzoquinones from para-substituted lignin model phenols. We reported some of the first examples of this transformation by converting S lignin models to dimethoxybenzoquinone (DMBQ, 4) and G lignin models to monomethoxybenzoquinone (MMBQ, 5). Although the oxidation proceeds in good yield for the production of 4, catalyst 1 gives low yields of 5 from oxidation of G model phenols. However, the yield of 5 from G models is improved when the reaction is supplemented with a sterically hindered, non-coordinating aliphatic base, such as DIPEA.

Recently, we reported that appending the hindered base to an aromatic ring of the Schiff-base ligand (e.g., complex 7) markedly improves yields, reaction times and catalyst loadings for the oxidation of both S and G model monomers and dimers in the absence of an added external ligand. The results suggest that the presence of a bulky aliphatic base bound in close proximity to the Co-superoxo complex promotes the formation of the phenoxy radical 3 through formation of an easily oxidized phenoxy intermediate 6. Parallel computational results on the reactivity of 1 in the presence of a series of substituted imidazoles as axial bases further suggest that the steric environment around the Co influences the geometry and reactivity of 2.

Based on these results, we wished to examine how synthetic design of the steric and electronic environment about the Co center in second-generation oxidation catalysts such as 7 could be exploited to optimize the reactivity of the complex. We report the synthesis and reactivity of a new family of unsymmetrical Co-Schiff base complexes bearing hindered, aliphatic nitrogen bases on the ligand’s ethylenediamine bridge as well as their use as catalysts for oxidation of primary lignin models in the presence of molecular oxygen. We further present preliminary computational results regarding the effect of the intramolecular base near the Co center and its impact on the mechanism of oxidation.

**Experimental**

**General information**

Specific details and analytical data for synthesis of new catalysts are available as ESI.† All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Anhydrous tetrahydrofuran (THF) was purified by distillation over sodium/benzophenone. All reagents and solvents were purchased from commercial sources and were used as received. Analytical thin layer chromatography (TLC) was performed using 250 m silica gel 60 F254 pre-coated plates. Flash column chromatography was performed using 230–400 mesh 60 A silica gel. The eluents employed are reported as volume: volume percentages. Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. Catalytic oxidations were carried out in thick walled glass reactors under the oxygen pressure indicated in the text. 1H and 13C NMR spectra were measured in CDCl3 using a Varian Unity 400 MHz instrument. Chemical shifts are reported relative to tetramethylsilane or solvent resonance and reported in ppm. Infrared spectra were obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer at 4 cm⁻¹ resolution and are reported in cm⁻¹. High resolution mass spectra (HRMS) were obtained by The Center for Mass Spectrometry of the Department of Chemistry at the University of Tennessee, and are reported as m/z (relative ratio). Accurate masses are reported for the molecular ion [M + H]+ or a suitable fragment ion and are reported with an error <5 ppm. 1-Octy1piperazine 15b, 1-methylpiperazine 15c, 1-phenylpiperazine 15d and piperidine 15e were purchased from Sigma-Aldrich and used as received.

2,3-Bis(3,5-di-tert-butyl-2-hydroxybenzylidene)amino)-propan-1-ol (13). To a solution of 2,3-dibromopropanol 8 (2.179 g, 10 mmol) in dry DMF (60 mL) was added NaN₃ (6.500 g, 100 mmol). The reaction mixture was heated at reflux under N₂ for 24 hours (dark brown), cooled to room tempera-
ture and treated with water (100 mL). The crude product was extracted with EtOAc (2 x 100 mL), rinsed with water (2 x 100 mL), dried over Na₂SO₄ and concentrated to afford a mixture of diazide 9 and 2-bromoprop-2-en-1-ol 10²¹ (10/1) as a light brown oil which was used in the next step without further purification; 2,3-diazidopropan-1-ol 9: 1H-NMR (400 MHz, CDCl₃): δ 7.37–3.62 (m, 3H), 3.47 (d, J = 18.1, 4.4 Hz, 2H); 13C-NMR (100 MHz, CDCl₃): δ 62.6, 62.4, 51.7. When non-dry DMF was used as solvent, 1,3-diazidopropan-2-ol was isolated as the major product: 1H-NMR (400 MHz, CDCl₃): 3.95–3.91 (m, 1H), 3.42–3.36 (dd, J = 7.8 Hz, 4H); 13C-NMR (100 MHz, CDCl₃): δ 69.8, 54.1.

To a solution of diazide 9 obtained above in THF–H₂O (50 mL, 4/1) was added Ph₃P (5.246 g, 20 mmol) portionwise at room temperature. The reaction mixture was heated at reflux for 6 h, concentrated under vacuum and the crude material purified by flash chromatography (gradient; 0–100% CH₂Cl₂–hexanes) to give 2,3-diaminopropan-1-ol as a thick green oil which was used in the next step without further purification. Presence of residual water or DMF in the crude material does not affect the yield of the next reaction.

To a solution of 11 obtained above in MeOH (50 mL) was added 3,5-di-tert-butyl-2-hydroxybenzaldehyde 12 (2.340 g, 10 mmol) in one portion. The reaction mixture was heated at reflux for 6 h, concentrated under vacuum and the crude material purified by flash chromatography (gradient; 0–50–100% CH₂Cl₂–hexanes) to give 13 as a thick bright yellow oil (2.103 g, 41%) which slowly solidified over time; mp 91 °C; 13C-NMR δ 167.1, 158.3, 158.2, 140.2, 140.2, 138.4, 136.8, 136.7, 129.4, 128.4, 127.2, 127.2, 127.1, 126.4, 126.2, 118.1, 118.0, 67.5, 63.3, 63.0, 62.1, 54.0, 53.4, 53.2, 53.1, 29.6; HRMS (DART-TOF) Calcd for C₁₄H₁₄N₂O₂ (M + H): 261.51075; found 261.50843.

Cobalt-Schiff base complex 17a. To a solution of Schiff base 16a (121.3 mg, 0.18 mmol) in i-propanol (2 mL) was added a solution of Co(OAc)₂·4H₂O (44.3 mg, 0.18 mmol) in methanol (1 mL). The mixture was heated at reflux for 3 h under argon. The dark brown solution was concentrated and the product was precipitated in 15 mL of hexanes. The green brown solid was recovered by filtration, rinsed with hexanes and then dried under vacuum for 24 h (dark orange), quenched by addition of water (30 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The organic fractions were combined, dried over Na₂SO₄, concentrated under vacuum and the crude product purified by flash chromatography (gradient; 0–2% MeOH–CH₂Cl₂) to give the product as a thick bright yellow oil (376 mg, 65%) which slowly solidified over time; mp 91–93 °C; Rf = 0.10 (100% CH₂Cl₂); IR (neat) 2952, 2866, 2807, 1640, 1443, 1360, 1252, 1176, 830, 736, 698 cm⁻¹; 1H-NMR (400 MHz, CDCl₃); δ 13.68 (bs, 1H), 13.56 (bs, 1H), 8.34 (s, 1H), 8.33 (s, 1H), 7.34–7.04 (m, 7H), 7.04 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 4.09 (dd, J = 12.0, 2.4 Hz, 1H), 3.75–3.60 (m, 2H), 3.49 (s, 2H), 2.73 (dd, J = 13.2, 6.8 Hz, 1H), 2.60–2.46 (m, 5H), 1.42 (s, 9H), 1.41 (s, 9H), 1.27 (s, 9H), 1.26 (s, 9H); 13C-NMR (100 MHz, CDCl₃): δ 167.8, 167.1, 158.3, 158.2, 140.2, 140.2, 138.4, 136.8, 136.7, 129.4, 128.4, 127.2, 127.2, 127.1, 126.4, 126.2, 118.1, 118.0, 67.5, 63.3, 63.0, 62.1, 54.0, 53.4, 53.2, 53.1, 29.6; HRMS (DART-TOF) Calcd for C₁₄H₁₄N₂O₂ (M + H): 681.51075; found 681.50843.

General procedures for the oxidation of p-phenols to benzoquinones

In a Fisher-Porter bottle, p-phenol substrate (1 mmol) and Cob-schiff base complex 17a-f (0.05 mmol) were combined in 5 mL of MeOH or 5 mL of MeOH–CH₂Cl₂ (4/1) for catalyst 22. The bottle was flushed with oxygen three times and then pressurized with oxygen to 50 psi. After 16 hours under vigorous stirring, the reaction mixture is concentrated under vacuum at room temperature and the crude material purified by flash chromatography (eluent: gradient 0–5–10% EtOAc–CH₂Cl₂); 2,6-Dimethoxybenzoquinone 4 (bright yellow) was recovered by filtration at the end of the reaction and satisfactorily matched
2,6-Dimethoxybenzoquinone is only partially soluble in methanol, and between 5 and 10% of residual product remains in solution that can be purified by column chromatography (elucent: gradient 0–5–10% EtOAc–CH₂Cl₂). When catalyst 22 was used, the reaction mixture was concentrated under vacuum and purified by flash chromatography (elucent: gradient 0–5–10% EtOAc–CH₂Cl₂). When catalyst 22 was used, the reaction mixture was concentrated under vacuum and purified by flash chromatography (elucent: gradient 0–5–10% EtOAc–CH₂Cl₂). 2-Methoxybenzoquinone 5 (light green) was purified by flash chromatography (elucent: gradient 0–5% EtOAc–CH₂Cl₂) and satisfactorily matched all previously reported data.

**Computational methodology**

All calculations were performed at the M06-2X level of theory with a mixed basis set using 6-31G(d) for C, H, N, and O and the LANL2DZ basis set for Co. Full geometry optimizations were carried out. The structures were modeled as neutral doublets (i.e., a single unpaired electron) with unrestricted calculations done for each structure. All calculations were done using Gaussian 09, revision B.01.

**Results and discussion**

New Co-Schiﬀ base complexes 17a–f were prepared in 6 synthetic steps from inexpensive, commercially available 2,3-dibromopropanol 8 (Scheme 1). Compound 8 was treated with an excess of sodium azide in dry DMF to afford a 90:10 mixture of diazidopropanol 9 and elimination product 10. Substitution of alkyl bromides with azide is normally reported using water or absolute ethanol as solvent, but under those conditions, we instead observed rapid formation of symmetrical 1,3-diazidopropan-2-ol as the primary product via intermediate 1-bromo-2,3-epoxypropane. Reduction of 9 to 2,3-diaminopropanol 11 was carried out using Staudinger conditions in the presence of triphenylphosphine. Compound 11 was condensed with aldehyde 12 to afford unsymmetrical Schiff base 13 in 41% yield over three steps. To the best of our knowledge, the only reported preparation of such 2,3-diaminopropanol-based salen structures requires multiple steps starting from costly 2,3-diaminopropionic acid.

**Scheme 1**

Co-Schiﬀ base complex synthesis. Reagents and conditions: (a) NaN₃, DMF, 70 °C, 16 h; (b) Ph₃P, THF–H₂O, reflux, 5 h; (c) 12, MeOH, reflux, 1 h (41%, 3 steps); (d) MsCl, Et₃N, CH₂Cl₂, rt, 1 h (95%); (e) 15, DIPEA, MeCN, reflux, 16 h (65–85%); (f) Co(OAc)₂·4H₂O, MeOH, reflux, 3 h (73–91%).
sions between 72–92% for 18 and 68–81% for 19, affording DMBQ 4 and MMBQ 5 as primary products. Aldehydes 20 and 21 were observed as side products along with unreacted starting material. As was observed with structurally related catalysts such as 7, an external axial base was not required in these oxidations. Indeed, addition of excess pyridine to an oxidation of G model (entries 4, 5, 10 and 11). Interestingly, the piperazinyl substituent appears to have a greater positive impact on the overall reactivity of these catalysts was lower than complex 7, 12 and 13). Although the reactivity of 20, which retains many of the steric features of the new catalysts also consistent with suppression of the oxidation using catalyst 17a (Fig. 3).

Computational analysis (DFT: M06-2X with the LANL2DZ basis set on the cobalt and 6-31G(d) basis set for all other elements) was used to examine these reactivity differences by comparing different conformations of catalyst 17a (Fig. 3).

The exo conformation reduces crowding around the Co, but is calculated to be 11.24 kcal less stable than the conformation placing the substituent endo to the Co. In the endo conformation, the piperazine nitrogen closest to the Schiff base ligand restricts access to the Co, but is also is within coordination distance (2.45 Å), which stabilizes the complex. Similar intramolecular binding has been observed for Co-Schiff base complexes such as 23 bearing an alkoxymethyl group in the same position as the piperazine substituent in 17a. The increased crowding around the Co resulting from this intramolecular coordination may contribute to the diminished reactivity observed with catalysts such as 17a when compared to more active catalysts such as 7 as formation of superoxo intermediate 2 (Fig. 1) could be slowed. This observation is also consistent with suppression of the oxidation using catalyst 17b in the presence of excess pyridine, as the pyridine would occupy the remaining axial site on the Co and prevent binding of O2 to form 2 (Table 1, entry 3).

The steric environment about the metal for these complexes may also be compared with Jacobsen’s Mn-Schiff base asymmetric epoxidation catalysts, which employ the same

Table 1  Catalytic oxidation of 18 and 19 with Co-Schiff base complexes 17a–d

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<th>Entry</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>4/5&lt;sup&gt;a&lt;/sup&gt; (%)</th>
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<sup>a</sup> Yields are given for isolated materials. <sup>b</sup> 100% pyridine was added to the reaction. <sup>c</sup> 10 mol% of catalyst used. <sup>d</sup> 100% DIPEA was added to the reaction.
ligand as 22 and possess a steric barrier at their periphery as a result of the array of t-Bu groups. In these catalysts, the preferred trajectory for approach of a substrate to the central metal is across the face of the ligand’s cyclohexyl group. The endo conformation of catalysts 17a-d places a substituent along this trajectory, resulting in a reduction of the catalyst’s reactivity.

Comparative DFT evaluation of the more reactive catalyst 7 supports this hypothesis as its low energy conformation, in contrast to 17a, places the piperazine nitrogens well outside of bond distance to the Co. Examination of several alternate (and higher energy) conformations of 7 gives a calculated Co–N distance no less than 4.8 Å. Complex 7 thus retains steric features similar to Jacobsen’s catalyst that would not significantly affect access to the Co.

The computational results also support the mechanistic scheme in Fig. 2. The ability of catalysts 17a-d to oxidize both S and G lignin models is critical to their eventual utility for conversion of biorefinery lignin. The improved oxidation of G models that results by incorporating a hindered base within the catalyst structure may result from deprotonating the substrate in close proximity to the intermediate Co-superoxo linkage. This deprotonation enhances formation of the reactive phenoxy radical from the resulting phenoxide anion and linkage. This deprotonation enhances formation of the reactive substrate in close proximity to the intermediate Co-superoxo complex. This deprotonation enhances formation of the reactive substrate in close proximity to the intermediate Co-superoxo complex. Such deprotonation may play a lesser role with S models. The presence of an additional OMe group on the aromatic ring can increase the rate of hydrogen atom removal by more than 100×, leading to a much more facile formation of phenoxy radicals from S models by direct hydrogen atom removal by the Co-superoxo complex 2. Thus, increased crowding of the coordination environment around the Co may affect loss of the hydrogen atom, which is reflected in the lower oxidation yields. Nonetheless, because the pKₐ values for 18 and 19 are almost identical (9.87 and 9.78), either substrate should undergo similar deprotonation, and the phenoxide derived from 18 may be contributing to the reaction.

Conclusions

Catalysts for lignin transformation will be most effective if designed to react with those functional groups present in highest concentration after lignin is isolated from renewable carbon sources. Our work is demonstrating that a focus on phenol oxidation, rather than β-aryl ether cleavage, is more representative of the actual functional group profile to be found in isolated, technical lignin. Further, the reactivity of these catalysts can be tuned by proper choice and position of sterically demanding groups within the structure of the ligand around the Co center. Incorporating a piperazinyl unit as part of the ligand increases the reactivity of the catalysts toward lignin G models without loss of reactivity toward S models. Our computational results also begin to clarify the mechanism of the process, and indicate how controlling access to the Co through ligation or steric crowding at the Co center can affect catalyst reactivity. These features will be critical in designing catalysts most effective for oxidation of all primary structural units in biorefinery lignin.

It is notable that these complexes induce oxidation in the absence of an added axial base, and that the addition of pyridine significantly inhibits quinone formation. Intramolecular coordination of the piperazine to the Co may activate binding to O₂ in a manner similar to complexes like Co(salpr) (24), particularly since computational results show such coordination...
to be energetically favorable.

Related Co catalyzed oxidations have been reported that do not require added axial base. However, these reactions are carried out under markedly different conditions in aqueous media and high pH, resulting in the presence of a high concentration of OH− ions. The suggested mechanism is likely quite different from that occurring in nonaqueous media. Moreover, the effectiveness of catalysts 7 and 22 suggest that coordination of an axial ligand may not be required for catalytic activity under these reaction conditions. In the case of 22, our current results suggest that a non-coordinating aliphatic base is sufficient to promote formation of radical intermediate 3 and subsequent rearrangement to para-benzoquinones. The increased overall size of the Schiff base ligand in both 7 and 17a–d may also be impeding catalyst deactivation pathways (such as formation of Co-peroxo dimers) that are easier with simpler complexes such as 1. The impact of these various factors on the reaction mechanism and design of catalysts with higher reactivity and their use for oxidation of biofinery lignin are under current active investigation.

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Notes and references


