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Catalytic oxidation of *para*-substituted phenols with cobalt–Schiff base complexes/O_2—selective conversion of syringyl and guaiacyl lignin models to benzoquinones

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ABSTRACT

Models of guaiacyl (G) and syringyl (S) subunits in lignin have been catalytically oxidized to their corresponding *p*-quinones in the presence of molecular oxygen. The oxidation of syringyl-like phenols readily occurred with 5-coordinate cobalt catalysts on which one of the ligands is a monodentate pyridine or imidazole base that coordinates axially to the metal. Formation of *p*-quinones with this system depends on the coordination of the axial base to the metal as influenced by its pK_a and its size. The yield of *p*-quinones from guaiacyl models was markedly improved by the addition of a sterically hindered aliphatic nitrogen base that *does not* coordinate to the catalyst. A mechanism involving deprotonation of the phenol substrate by the bulky base is proposed.

Introduction

Cobalt–Schiff base complexes have been extensively used to catalyze oxygen activation in the oxidation of phenols.[1–4] However, the use of these complexes for the oxidation of *p*-substituted phenols as models of catalytic conversion of lignin within the biorefinery has not been widely studied. Lignin, which comprises nearly 25% of terrestrial biomass, remains one of the most underused renewable carbon sources in the biosphere because of its structural heterogeneity and lack of processes able to convert it into a single material in high yield. Lignin's heterogeneity results from free radical polymerization of monomeric, *p*-substituted guaiacyl (G), *p*-hydroxyphenyl (H), and syringyl (S) units (Fig 1). Biosynthesis of lignin from these monolignols results in a wide variety of substructural units connected through ether and carbon–carbon linkages.[5]

As part of our program to develop a synthetic methodology for the conversion of renewable carbon sources into biobased chemicals, we reported that O_2 (50–60 psi) in the presence of 5–10% Co(salen) and pyridine or Co(*N*-Me salpr) (**1** and **2**, Fig. 2) in MeOH at room temperature converted syringyl alcohol (**3**, 3,5-dimethoxy-4-hydroxybenzyl alcohol) and several other *p*-substituted phenols that model lignin's S units into 2,6-dimethoxybenzoquinone (DMBQ) in high yield.[2] However, oxidation of compounds modeling the less electron-rich G units in lignin, such as 3-methoxy-4-hydroxybenzyl alcohol (**4** or vanillyl alcohol), proceeded in much lower yield.

To expand the utility of this process to a wider range of lignin's substructural units we have examined the reactivity of the

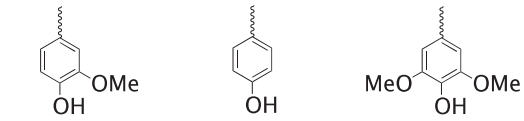

Figure 1. The primary monomeric units in lignin.

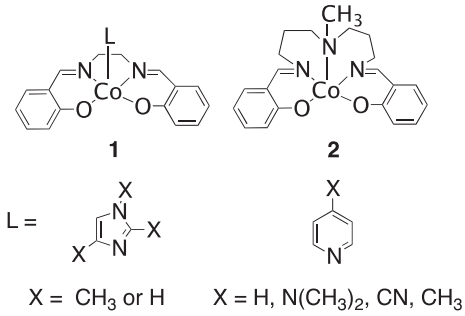

Figure 2. Complexes and ligands used in this study.

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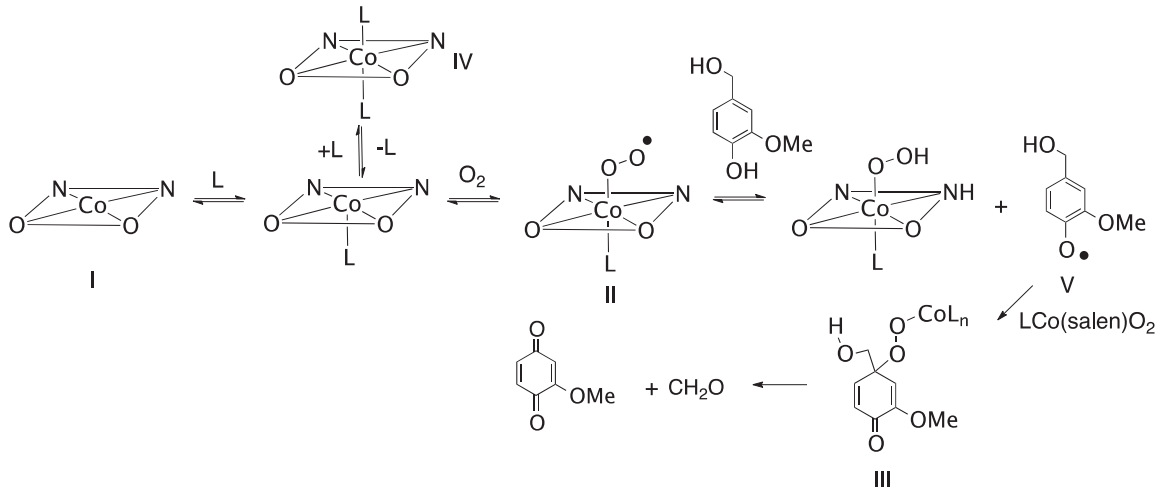


Scheme 1. Mechanism for *p*-quinone formation from *p*-substituted phenols catalyzed by **1**.

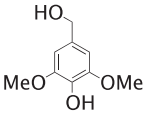
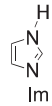
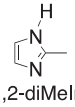
catalytically active complex in the presence of added aromatic or aliphatic nitrogen bases. We now report that the yield of quinone from the oxidation of several lignin models catalyzed by **1** or **2** is strongly affected by the addition of a series of structurally diverse aromatic nitrogen-containing ligands and that oxidation of vanillyl alcohol is markedly improved in the presence of sterically hindered aliphatic nitrogen bases.

Results and discussion

Oxidation of syringyl unit models

The ability of Co(salen) derivatives to reversibly bind oxygen and form superoxo complexes in solution is well established.[6–9] The oxygen binding ability is strongly enhanced by the addition

Table 1
Co(salen) catalyzed oxidation of syringyl alcohol (**3**)

Substrate	Added imidazole	Conjugate acid pK_a[a]	DMBQ yield (%,10:1 L:C)[b]	DMBQ yield (%, 1:1 L:C)[b]	Added pyridine	Conjugate acid pK_a[a]	DMBQ yield (%)[b]
 **3**		5.03[c]	30	31	 4-MePyr	6.04	74
	 Im	7.00	<5	5[d]	 Pyr	5.24	82
	 1-MeIm	7.33	29	69			
	 1,2-diMeIm	7.85	67	63	 DMAP	4.48	50
	 2,4-diMeIm	8.00	72	65	 4-CNPyr	1.64	64
	 2,4-diMeIm	8.52[e]	71	67			

[a] Grimmett, M. R. *Adv. Heterocycl. Chem.* **1980**, *27*, 242.
[b] Isolated yeild; av. for 3 runs.
[c] Brown, R. S., Clewly, R. G. *J. Org. Chem.* **1987**, *52*, 1216.
[d] After 24 h
[e] Nozaki, Y.; Gurd, F. R. N.; Chen, R. F.; Edsall, J. T. *J. Am. Chem. Soc.* **1956**, *79*, 2123.

of a monodentate nitrogen-containing base as **1** by itself binds oxygen poorly.[10] The Co(salen)/ligand/O_2 adduct has been effectively used for synthesizing benzoquinones from phenolics unsubstituted in the position *para* to the hydroxyl group (Scheme 1).[11–14]

In these reactions, the added ligand coordinates to the Co–Schiff base complex (I), which subsequently coordinates a molecule of dioxygen. The resulting Co(salen) superoxo adduct (II) abstracts a hydrogen from the phenolic substrate to generate a phenoxy radical which reacts with a second molecule of II and via rearrangement of the resulting intermediate III, forms a *p*-quinone. We investigated whether modifying the added ligand would improve the ability of complex II to abstract a hydrogen atom from the phenol substrate, leading to higher yields of quinone. Table 1 summarizes the effect of a series of imidazole and pyridine bases on the yield of quinone from the oxidation of **3** catalyzed by **1**.

When using a 10:1 excess (ligand:catalyst, L:C) of several imidazole ligands, the yield of quinone[15] correlates with the pK_a of the imidazole's conjugate acid, plateauing with 1,2-dimethylimidazole. These results show that as the basicity and corresponding donor ability of the imidazole ligand increases, the dioxygen affinity of the Co complex and its ability to abstract a hydrogen atom from the starting phenol also increases. Correspondingly, we observe that the yield of DMBQ decreases when using 1-acetyl-2-methylimidazole[16] as the axial ligand. The poorer donor ability of this ligand destabilizes the formation of the dioxygen complex and reduces the yield of *p*-quinone.[17] The low DMBQ yield observed with excess Im and 1-MeIm likely results from preferential formation of an inactive bis-imidazole complex that cannot bind oxygen to form the catalytically active Co–superoxo complex.[18]

When the L:C ratio is reduced to 1:1, the yield of DMBQ increases significantly using 1-MeIm as a ligand. However, we also observe a slight reduction in DMBQ yields with 2-MeIm, 1,2-diMeIm, or 2,4-diMeIm, suggesting that the correlation of yield with ligand donor ability is tempered by the size of the added axial ligand. X-ray analysis of several Co–Schiff base complexes reveals that binding to an axial base distorts the square pyramidal geometry about the metal by pushing the Co out of plane. This distortion forces the Schiff base ligand to adopt an 'umbrella' shape, with the extent of the distortion being greater for bulkier ligands.[19] For the smaller ligands in this study (Im, 1-MeIm), this distortion is insufficient to preclude formation of a bis-imidazole complex at high L:C ratios, but lower L:C ratios allow a shift of the equilibrium between the different Co complexes in solution away from bis-imidazole adducts. With the larger ligands (2-MeIm, 1,2-diMeIm or 2,4-diMeIm), the methyl groups flanking the coordinating nitrogen induce a greater distortion in the salen ligand upon binding. As a result, binding of a second bulky ligand to the metal center at either L:C ratio is inhibited. However, employing lower L:C ratios with the larger ligands also affects the equilibrium between the Co complexes in solution, in this case, reducing the relative amount of Co–superoxo complex present, and thus, slightly reducing the observed DMBQ yield.

In contrast to substituted imidazoles, we find a poorer correlation of oxidation yields and pK_a when substituted pyridines are added as ligands (Table 1). With the exception of 4-dimethylaminopyridine (DMAP), which undergoes competitive formation of an unreactive binuclear dioxygen complex in solution,[20] addition of 4-methylpyridine (4-MePy), 4-cyanopyridine (4-CNPy), or pyridine (Pyr), all lead to >60% yield of DMBQ regardless of the ligand's pK_a. As with reactions in the imidazole series, poorer donors (e.g., 4-CNpy) lead to lower DMBQ yields. Since the pyridine series contains only *p*-substituted materials, effects from steric interaction of each ligand with the Co center would be approximately the same, and thus, low L:C ratios did not increase the yield of DMBQ. The lower donor ability of substituted pyridines when compared to imidazoles[21] apparently minimizes catalyst deactivation via the formation of bis-pyridine adducts.

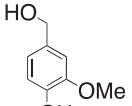
Oxidation of guaiacyl unit models

Although S subunit models were easily converted into their corresponding *p*-quinones with **1** or **2**, the same approach with vanillyl alcohol, a model of the G subunit in lignin gave the corresponding 2-methoxybenzoquinone (MMBQ) in only 21% yield. G models are more difficult to oxidize than S models (Fig 1) because formation of the key phenoxy radical (Scheme 1, V) is slower.[22,23] Attempts to improve these yields have had little success.[24] However, we find that the yield of MMBQ from vanillyl alcohol is significantly improved by adding a sterically hindered base such as *N*,*N*-diisopropylethylamine (DIPEA), diisopropylamine (DIPA), or triethylamine (TEA) to oxidations catalyzed by **1** or **2** (Table 2).

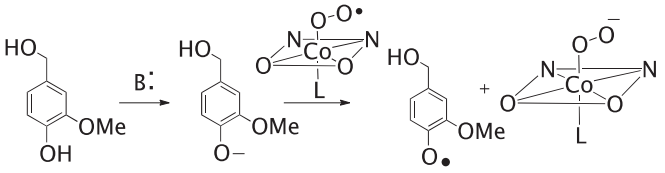
These bases, each with a pK_a ~10–11 lead to yields of MMBQ of 52–55% in the presence of 10% of **2**. Reactions with 10% Co(salen) yielded similar results in the presence of DIPEA and DIPA. We observe a limit to the basicity of the hindered amine as DBU and DABCO (pK_a = 13.28 and 8.19, respectively) either led to decomposition of the starting phenol, or did not improve the MMBQ yield. These results are consistent with previous findings using Na_2CO_3 as the base.[4] Importantly, the addition of a sterically hindered base does not reduce the yield of DMBQ from S models. Oxidation of **3** using catalytic amounts of Co(salen) and equimolar amounts of diisopropylethyl amine (DIPEA) give a 67% yield of DMBQ while oxidation of syringaldehyde (3,5-dimethoxy-4-hydroxybenzaldehyde) in the presence of Co(salen) and triethylamine (TEA) gives a 73% yield of DMBQ.

In order to assess the involvement of the sterically hindered base in the presumed mechanism (Scheme 1), we studied the interaction between DIPEA and Co(salen) using NMR and UV–vis spectroscopy (Supplementary data). The ^{1}H NMR spectrum of paramagnetic Co(salen) in CD_2Cl_2 exhibits chemical shift values similar to those reported for the same complex in other non-coordinating solvents such as $CDCl_3$[25,26] and DMSO-d_6.[27] However, upon addition of pyridine, the ^{1}H signals of Co(salen) undergo a dramatic shift, suggesting strong interaction or coordination with the added ligand. In contrast, addition of DIPEA does not affect the position of the Co(salen) peaks. UV–vis spectra also reflect significant changes only when pyridine is progressively titrated into a sample of a fixed concentration of Co(salen) in CH_2Cl_2. Alternatively, titration with DIPEA leads to no changes in the spectrum.

Table 2
Oxidation of **4** in the presence of sterically hindered bases. Reaction conditions: 10 mol % of hindered base and Co(*N*-Me salpr)

Substrate	Hindered base	Conjugate acid pK_a[a]	yield (%)[b]
 **4**	None	–	21
	DABCO	8.19	21
	DIPEA	10.98	55
	DIPA	10.76	51
	TEA	10.60	52
	DBU	13.28	0[c]

[a] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02. pKa of the most basic site at temperature = 25 °C.
[b] Isolated yield reported.
[c] A complex polymeric mixture was isolated with complete consumption of starting material.



Scheme 2. Proposed mechanism for the oxidation of guaiacyl models in the presence of a hindered base.

Furthermore, the success of **2** in these reactions mitigates against binding of the hindered base, as such binding would likely preclude addition of O_2 by blocking the available coordination site. These findings suggest that the bulky aliphatic bases used in this study *do not* bind to the catalyst and thus their role must involve other mechanistic pathways (Scheme 2).

Our proposed mechanism involves deprotonation of the substrate by the sterically hindered base to form a more readily oxidized phenolate anion.[28] The resulting anionic Co intermediate is protonated and subsequently decomposed to hydroperoxy radical and III. The phenoxy radical undergoes conversion to MMBQ, formaldehyde, and Co(*N*-Me salpr)-OH as shown in Scheme 1.

Addition of hindered bases to the oxidations of other G models such as isoeugenol, eugenol, vanillin, and vanillin acetal[29] gave only low yields (0–10%) of MMBQ. Currently the reason for this behavior is not yet clear, but may be related to the release of formaldehyde from a benzyl-type substrate rather than the release of other small molecules, for example, CO from vanillin (Scheme 1). Ample and fairly recent EPR evidence suggests that phenoxy radicals can also coordinate to cobalt–Schiff base complexes.[30,31] Our studies with **2** suggest that at least initially, coordination of the substrate is not necessary for the reaction. Further investigation into this alternative mechanism and computational evaluation of the intermediate Co complexes is currently underway.

Conclusions

The effect of a series of aromatic and sterically hindered aliphatic bases on the yield of oxidation of G and S lignin models in the presence of catalytic amounts of cobalt–Schiff base complexes is influenced by both electronic and steric effects. S models give a higher yield of *p*-quinone with imidazole ligands of higher pK_a at high L:C ratios, reflecting the donor ability of the ligand. However, at lower L:C ratios, steric effects emerge for imidazole ligands bearing methyl groups adjacent to the ligating nitrogen. Addition of a bulky aliphatic base increases the yield of *p*-quinone when vanillyl alcohol (a G model) is used as the substrate in the presence of **1** or **2**, but importantly, does not decrease the yield of quinone formation from S models. We propose a plausible mechanism in which the sterically hindered base *does not* coordinate to the catalyst but rather deprotonates the substrate in order to ease its oxidation. Future work will be directed toward the applications of our oxidation conditions to natural lignin and EPR identification of the intermediates involved in the reaction.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures for oxidation of substrates, UV–vis and ^{1}H NMR spectra for Co complexes) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.093.

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15. These oxidations primarily lead to the formation of DMBQ from **3** and MMBQ from **4**. The other isolated product is unreacted starting material. During the oxidation of **3** we also observed incomplete oxidation represented by the formation of syringaldehyde (detected by ^{1}H NMR) in $\leqslant$20% yield.
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