

Oxidative N-dealkylation in cobalt–bispidine–H₂O₂ systems†

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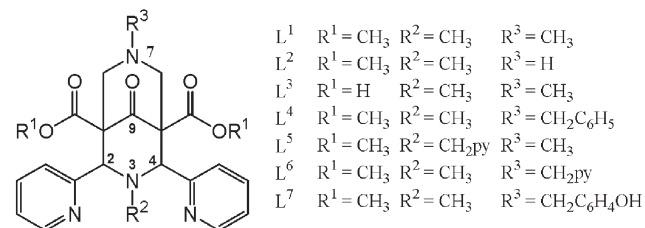
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The reaction of the Co^{II} complex with the rigid bispidine ligand L¹ with two tertiary amine and two pyridine donors, [Co^{II}(L¹)(OH₂)₂]²⁺, with H₂O₂ and O₂ produces [Co^{III}(L²)(OH₂)₂]³⁺, where L² is demethylated at one of the amine donors, and CH₂O.

Oxidative N-dealkylation is a major pathway for drug metabolism, and this may involve various peroxidase or oxidase enzymes, such as lipogenase, horseradish peroxidase, bleomycin, methemoglobin, cytochrome P450 and amine oxidases.¹ Dehydrogenation (metal-based one-electron transfer) or H-atom abstraction (C-based radical mechanism) pathways have been proposed and studied in detail.² A number of low molecular weight model complexes, primarily with Fe and Co, have been shown to mimic these processes with either dioxygen or peroxide as oxidant and in the H-atom abstraction or electron transfer mode; this has not been studied in detail in many examples.³ There are a few examples with oxidative N-dealkylation in cobalt-based systems;⁴ but the cobalt/dioxygen (hydrogen peroxide) chemistry is generally dominated by the formation of μ -peroxo- and μ -superoxo dicobalt(III) complexes and their hydrolysis to mononuclear Co^{III} products; μ -peroxo-dicobalt(II) and mononuclear Co^{II} as well as Co^{III} hydroperoxo complexes have been reported but only rarely been studied in detail.⁵

Bispidine ligands (see Scheme 1) are very rigid diazaadamantane derivatives which prefer relatively large metal ions;⁶ this is reflected by relatively high redox potentials, intermediate to low ligand fields, the stabilization of the reduced metal centers and high spin electronic configurations.^{6,7} Therefore, it is not surprising that Co^{II}–bispidine complexes are air stable.^{6,8} Here, we report the syntheses and structures of a number of bispidine Co^{III} and Co^{II}



Scheme 1

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† Electronic supplementary information (ESI) available: Syntheses and characterization, crystal structure determination and DFT calculations. Table S1: Electrochemical, spectroscopic and kinetic data. Fig. S1: Time-dependent UV-vis spectra for the oxidation of [Co^{II}(L¹)(OH₂)₂](ClO₄)₂ with H₂O₂ in MeOH under anaerobic conditions. Discussion of kinetics, labeling studies and hydrazine test. See DOI: 10.1039/b602571d

complexes and a mechanistic investigation of the oxidative N-dealkylation observed during the oxidation of the Co^{II} complexes of L¹ and L⁴ in MeOH with H₂O₂.

The reaction of K₃[Co(CO₃)₃] with L¹, yields [Co^{III}(L³)(CO₃)₃]⁺,⁹ that of [Co(L¹)(solvent)₂]²⁺ (MeOH, ambient atmosphere) with H₂O₂ produces [Co^{III}(L²)(X)₂]³⁺ (X = OH₂, Cl⁻). Reaction of the chloro complex with approx. 2 eq. AgClO₄ leads to substitution of Cl *trans* to N7 as the single product, indicating that donors *trans* to N3 are more strongly bound, as expected,^{7,14-16} and that the peroxide probably also is bound *trans* to N3. Plots of experimental X-ray structures are shown in Fig. 1 and selected structural data are given in Table 1.† The Co–N7 bond and N3⋯N7 bite distance in [Co^{II}(L¹)(OH₂)₂]²⁺ are larger than in [Co^{II}(L²)(OH₂)₂]²⁺. This trend is reproduced by DFT calculations (*a/a'*, *b/b'* in Table 1) and is also confirmed for Co^{III}.

Bispidine ligands are known to prefer relatively large metal ions and, for L¹ the metal-ion-enforced strain on the ligand has been computed to be around 15 kJ mol⁻¹ for Co^{III} vs. Co^{II}.⁶ Therefore, relatively low ligand fields and positive redox potentials are expected (for spectroscopic, electrochemical and kinetic data see ESI†). For L¹ and L² the Co^{III/II} couples are in a range, where it is expected that the Co^{II} complexes are air-stable (L¹, MeCN 653 mV; L², MeCN, 250 mV; vs. Ag/AgNO₃).

Oxidation of the Co^{II} bispidine complexes by H₂O₂ is a relatively slow process with pseudo-first order rates in the range of approx. (1–10) × 10⁻³ s⁻¹ (see Table S1 in ESI†); note that there is a faster initial reaction step which has not yet been analyzed (see ESI† Fig. S1 and S2). The most intriguing observation is that the oxidation with H₂O₂ leads to N-demethylation at N7 (transformation of L¹ to L²). A similar observation was made with the benzylated ligand (transformation of L⁴ to L²). The demethylated product (Co^{III} complex of L²) was identified by NMR spectroscopy and an X-ray crystal structure (see Fig. 1), preceded by the separation of the major from byproducts by ion exchange chromatography (approx. yield: 40% with 3 eq. H₂O₂, full conversion with ≥ 20 eq. H₂O₂, MeOH, ambient atmosphere). The organic product of the demethylation process is an aldehyde (formaldehyde with L¹, benzaldehyde with L⁴), characterized as the corresponding hydrazones (see ESI†).¹⁷

Interestingly, this reaction does not occur in the absence of air (dioxygen), which suggests that a carbon-based radical might be involved (autoxidation).¹⁸ No demethylation is observed in MeCN, and this might be due to a large shift of the redox potential (approx. 400 mV for L¹/L², see ESI†). Intermediates of the oxidative N-demethylation of L¹ and L⁴ have been studied by ESI-MS,¹⁹ and the assignments to cobalt oxo and cobalt peroxo species are supported by H₂¹⁸O₂ labeling studies (oxygenation of our cobalt(II) complexes; for *m/z* + 2, + 4, respectively), see ESI.† Based on these results, we propose a mechanism with a concerted

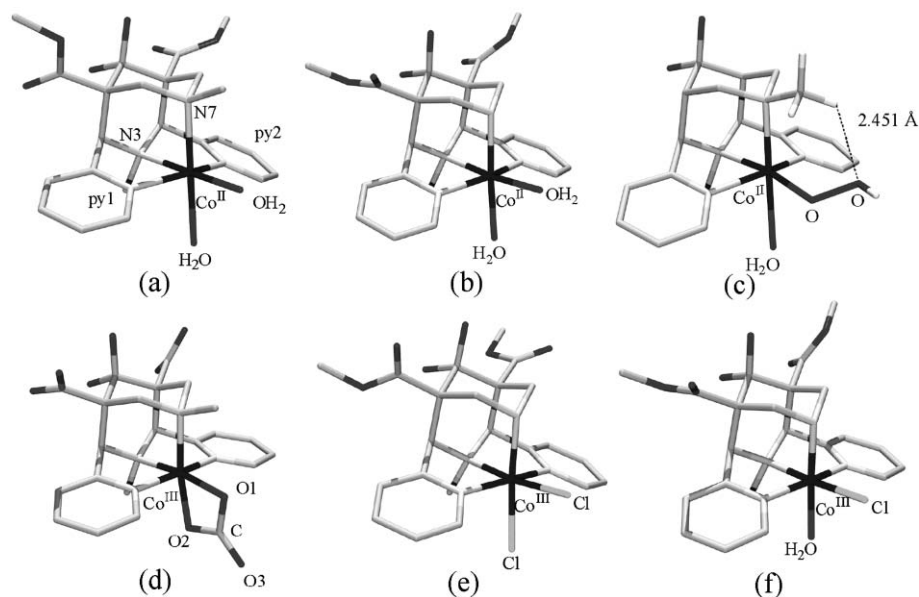


Fig. 1 Plots of the structures for the Co^{III} and Co^{II} complexes: (a) X-ray, [Co^{II}(L¹)(OH₂)₂](ClO₄)₂·H₂O·⁸; (b) X-ray, [Co^{II}(L²)(OH₂)₂](ClO₄)₂·4H₂O; (c) DFT [B3LYP/6-31G(d)], [Co^{II}(L¹)(OOH)(OH₂)]⁺; (d) X-ray, [Co^{III}(L³)(CO₃)]PF₆·3H₂O; (e) X-ray, [Co^{III}(L²)Cl₂](ClO₄)·1.5H₂O; (f) X-ray, [Co^{III}(L²)(Cl)(OH₂)](ClO₄)₂.

Table 1 Selected structural data of the Co^{III} and Co^{II} bispidine complexes; a' and b' are DFT-optimized structures of a and b [B3LYP/6-31G(d)]

	a ⁸	a'	b	b'	c	d	e	f
Co–N3	2.159(2)	2.129	2.115(4)	2.136	2.204	1.934(2)	1.965(6)	1.956(4)
Co–N7	2.218(2)	2.215	2.151(6)	2.183	2.224	2.036(2)	2.018(7)	1.979(4)
Co–py	2.087(2)	2.114	2.089(5)	2.119	2.108	1.925(2)	1.918(7)	1.925(4)
	2.120(2)	2.115	2.096(7)	2.120	2.162	1.928(2)	1.957(7)	1.945(4)
N3–N7	2.90	3.00	2.83	2.95	2.99	2.79	2.75	2.72
py1–Co–py2	153.13(7)	156.51	156.7(2)	156.18	151.18	169.82(10)	164.14(28)	167.26(18)

cobalt-based electron transfer and H-abstraction, involving the six-membered ring transition state shown in Scheme 2.

The putative Co^{II}–hydrogenperoxide intermediate [Co^{II}(L¹)(OOH)]⁺ was optimized by DFT (B3LYP/6-31G(d), see Fig. 1(c)). The main structural feature is a relatively short O···H contact (coordinated peroxide oxygen to the N7-methyl hydrogen atom, 2.45 Å), as required in the proposed mechanism.

Among external substrates, the tertiary amine *N*-benzyl-*N*-ethylaniline remained intact in solution with [Co^{II}(L¹)(OH₂)₂]²⁺ H₂O₂, MeOH. However, addition of the secondary amine *N*-benzylaniline produced benzaldehyde. As expected, dealkylation of L¹ also occurs in this reaction but in a significantly lower yield than without an external substrate.

The pentadentate ligands L^{5–7} are not dealkylated due to the significant structural and electronic changes at the sites *trans* to N3 and N7.²⁰ The failure to observe dealkylation in MeCN (stabilization of Co^{II}, see ESI†) and in reactions based on

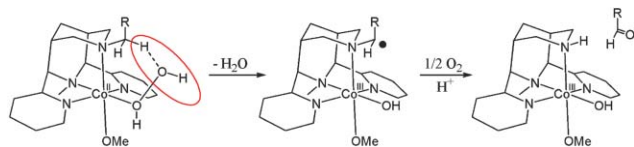
[Co^{III}(L³)(solvent)₂]³⁺ (prepared *in situ* from [Co^{III}(L³)(CO₃)]⁺) support the importance of the electron transfer step.

The fact that the reaction does not lead to full conversion with respect to the oxidative *N*-dealkylation (supported by kinetic traces which did not yield any isosbestic points), indicates that another oxidation process leading to Co^{III} products of L¹, probably involving the usual dinuclear μ-peroxo dicobalt complexes, competes with the dealkylation process.

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Notes and references

‡ [Co^{II}(L²)(OH₂)₂](ClO₄)₂·4H₂O: C₂₃H₂₉N₄O₁₇Cl₂Co, *M* = 763.33, triclinic, space group *P*1̄, *a* = 10.7753(8), *b* = 12.521(1), *c* = 15.259(1) Å, α = 91.266(2), β = 109.016(2), γ = 111.689(1)°, *V* = 1784.7(2) Å³, *Z* = 2, *T* = 100(2) K, 6313 independent reflections, *R*_{int} = 0.0401, θ_{max} = 25.03°, 401 parameters, *R*-values (*I* > 2σ(*I*)): *R*₁ = 0.1045, *wR*₂ = 0.3371. [Co^{III}(L³)(CO₃)]PF₆·3H₂O: C₄₄H₆₃N₈O_{27.5}K₃PF₆Co₂, *M* = 1524.16, triclinic, space group *P*1̄, *a* = 13.8467(8), *b* = 14.6159(9), *c* = 16.919(1) Å, α = 101.279(1), β = 111.414(1), γ = 107.638(1)°, *V* = 2851.2(3) Å³, *Z* = 2, *T* = 103(2) K, 19451 independent reflections, *R*_{int} = 0.0452, θ_{max} = 32.02°, 1111 parameters, *R*-values (*I* > 2σ(*I*)): *R*₁ = 0.0513, *wR*₂ = 0.1162. [Co^{III}(L²)Cl₂](ClO₄)·0.25CH₃CN: C_{22.5}H_{25.75}N_{4.25}O₁₀Cl₃Co, *M* = 681.00, triclinic, space group *P*1̄, *a* = 8.316(2), *b* = 12.937(3), *c* = 13.434(3) Å, α = 77.85(3), β = 76.36(3), γ = 82.11(3)°, *V* = 1367.3(5) Å³, *Z* = 2, *T* = 200(2) K, 4001 independent reflections, *R*_{int} = 0.0488, θ_{max} = 24.01°, 437 parameters, *R*-values (*I* > 2σ(*I*)): *R*₁ = 0.0577, *wR*₂ = 0.1632.



Scheme 2

[Co^{III}(L²)(Cl)(OH₂)](ClO₄)₂: C₂₂H₂₆N₄O₁₆Cl₃Co, *M* = 767.75, triclinic, space group *P* $\bar{1}$, *a* = 11.350(2), *b* = 13.262(2), *c* = 13.980(2) Å, α = 113.766(2), β = 91.005(3), γ = 109.556(2)°, *V* = 1786.3(4) Å³, *Z* = 2, *T* = 100(2) K, 6310 independent reflections, *R*_{int} = 0.0426, θ_{max} = 25.02°, 424 parameters, *R*-values (*I* > 2σ(*I*)): *R*1 = 0.0692, *wR*2 = 0.2001. CCDC 600455–600458. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b602571d

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