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Functional Synthetic Model for the Lanthanide-Dependent Quinoid Alcohol Dehydrogenase Active Site

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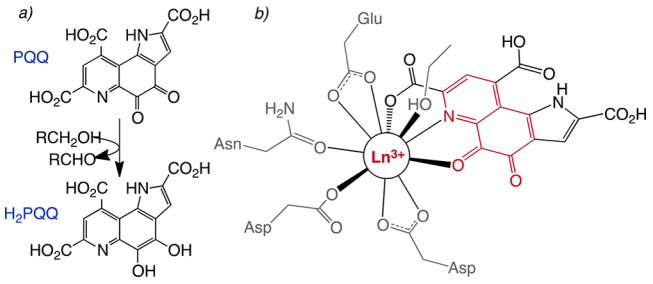
Supporting Information

ABSTRACT: The oxidation of methanol by dehydrogenase enzymes is an essential part of the bacterial methane metabolism cycle. The recent discovery of a lanthanide (Ln) cation in the active site of the XoxF dehydrogenase represents the only example of a rare-earth element in a physiological role. Herein, we report the first synthetic, functional model of Ln-dependent dehydrogenase and its stoichiometric and catalytic dehydrogenation of a benzyl alcohol. Density functional theory calculations implicate a hydride transfer mechanism for these reactions.

Methanol dehydrogenase (MDH) enzymes play an important role in the global carbon cycle, namely through the bacterial methane metabolism pathway, by catalyzing the oxidation of methanol.[1] The active site of MDH enzymes contains a pyrroloquinoline quinone (PQQ) cofactor bound to a Ca^{2+} ion, which accepts formally two electrons and two protons from an alcohol substrate to afford the corresponding aldehyde and catechol (H_2PQQ, Scheme 1a).[2] It was recently demonstrated that early lanthanide ions:

Scheme 1. (a) Reaction between Cofactor PQQ and Alcohol Substrates To Give Catechol H_2PQQ and (b) Active Site of Ln-Dependent MDH from XRD Data with Bound EtOH Ligand



La−Nd accelerated alcohol metabolism, and in one case were essential for cell growth of certain methanotrophic bacteria.[3] An X-ray structure of the XoxF-type MDH enzyme from *Methylacidiphilum fumariolicum* SolV revealed a Ln^{3+} cation bound by the PQQ cofactor (Scheme 1b),[3d] the first example of a lanthanide (or rare-earth) element in a physiological role. Lanthanides evidently confer a competitive advantage over Ca^{2+}, with XoxF-MDH displaying a 10-fold higher methanol affinity constant than Ca-MDHs.[3d,4] Furthermore, Ca-MDHs exhibit highest activities at pH ∼ 9 whereas XoxF-MDH functions optimally at neutral pH and does not require ammonium ions for activation.[3d,4] Also, in contrast to Ca-MDHs, XoxF-MDH catalyzes the oxidation of formaldehyde to formate.[3d,4]

The study of well-defined synthetic model compounds is essential for understanding the workings of enzyme active sites, which in turn may inspire novel catalysts.[5] At present, however, reports of synthetic metal complexes of PQQ or analogues are scarce[6] and only a handful of such compounds have been structurally characterized.[7] Furthermore, their reactivity has typically not been reported, with a few exceptions.[6a−e] To date, there are no reports of a synthetic lanthanide complex of PQQ or its surrogates.

There are a number of challenges associated with synthesizing analogues of MDH active sites. First, PQQ derivatives may coordinate to a metal ion in non-natural binding modes, such as through the two quinone oxygen atoms[7c,d] or the distal pyrrole and carboxylic acid groups.[7a] Multiple quinoline quinones (QQs) may also bind a single metal center or otherwise exhibit complicated speciation.[8] To overcome these potential problems, we designed the ligand L_{QQ} (Scheme 2), which incorporated a directing and sterically bulky chelator. An important goal of this design was the structural characterization of metal complexes of L_{QQ} and the product(s) of their reaction with substrates. We report herein the synthesis of L_{QQ}, its corresponding lanthanum complex $[La(L_{QQ})(NO_3)_3]$ and its stoichiometric and catalytic dehydrogenation of a benzyl alcohol substrate.

Proligand L_{QQ} was synthesized in 11 steps from commercially available starting materials (Scheme 2). Metalation of L_{QQ} proceeded smoothly using $[La(NO_3)_3(THF)_4]$ to obtain $[La(L_{QQ})(NO_3)_3]$ in 90% yield as a moisture-sensitive orange solid (Scheme 2). $[La(L_{QQ})(NO_3)_3]$ is a rare example of a metal complex of a quinoline quinone[7] and is the first such lanthanide complex. The X-ray crystal structure of $[La(L_{QQ})(NO_3)_3]$ revealed La(1) to bound to the pyridyl nitrogen atom N(1) and a single quinone oxygen O(1) of the QQ moiety (Scheme 2 and S1), analogous to the coordination environment of the XoxF enzyme active site (Scheme 1).[3d,4] Cyclic voltammograms (CVs) performed on L_{QQ} revealed a largely reversible process at $E_{1/2}$ = −0.95 V vs Fc/Fc^+ for the quinone−semiquinone ($QQ/QQ^{\bullet-}$) couple (Figure 1, dashed line) followed by an irreversible process at E_c = −1.76 V

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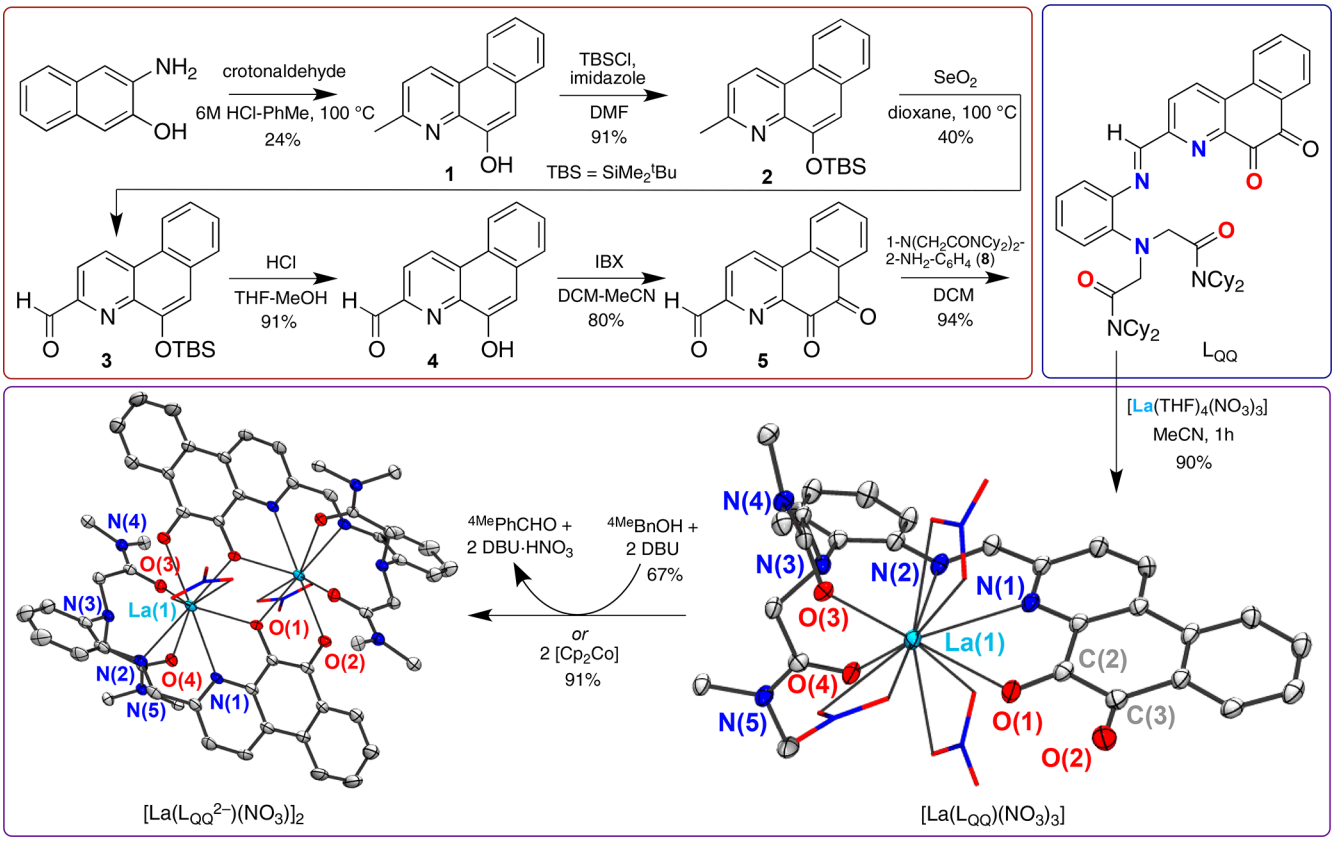
Scheme 2. Synthesis of L_{QQ}, $[La(L_{QQ})(NO_3)_3]$ and $[La(L_{QQ}^{2-})(NO_3)]_2$ with 50% Thermal Ellipsoid Plots[a]



[a]H-atoms have been omitted, cyclohexyl groups have been truncated and NO_3^- ligands are displayed in wireframe for clarity.

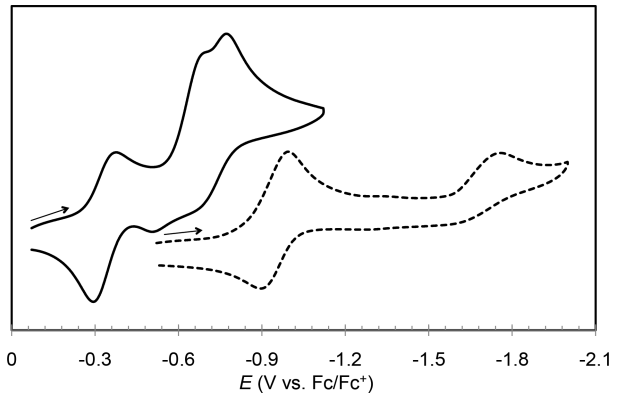


Figure 1. Cyclic voltammograms of $[La(L_{QQ})(NO_3)_3]$ (solid line) and L_{QQ} (dashed line) in CH_2Cl_2 with 0.1 M $[^nPr_4N][BAr^F{}_4]$ at a scan rate of 100 mV s^{-1}.

assigned as formation of the catecholate dianion (Q^{2-}).[9] For $[La(L_{QQ})(NO_3)_3]$, the $QQ/QQ^{\bullet-}$ couple was observed at +0.61 V higher potential ($E_{1/2}$ = −0.34 V; $i_a/i_c \approx 0.8$ at 100 mV s^{-1}, Figure 1, solid line.) Two poorly reversible, overlapping reduction events were revealed on further cathodic sweeps at −0.68 and −0.77 V, which showed return waves at −0.66 and −0.52 V. Overall, the CV of $[La(L_{QQ})(NO_3)_3]$ was complicated by loss of NO_3^- ligand(s) and dimerization equilibria (*vide infra*); the waves were not definitively assigned (Figures S31–36). Importantly, the anodic shift of the $QQ/QQ^{\bullet-}$ couple for $[La(L_{QQ})(NO_3)_3]$ compared to L_{QQ} reflected stabilization of the $QQ^{\bullet-}$ anion by the bound metal ion.[9a,10]

We expected that the relative ease of reduction of the QQ moiety upon coordination to La would be reflected in the ability of $[La(L_{QQ})(NO_3)_3]$ to oxidize an alcohol substrate. A CD_2Cl_2 solution of free ligand L_{QQ} with a 4-fold excess of ^{4Me}BnOH[11] gave no detectable aldehyde product by ^{1}H NMR spectroscopy, upon mixing, even after 3 days. In contrast, $[La(L_{QQ})(NO_3)_3]$ reacted with 2.5 equiv ^{4Me}BnOH in CD_2Cl_2 to produce ^{4Me}PhCHO in 30% yield in 24 h (67% yield in 3 days, Table S3). As observed by Itoh and Fukuzumi in a related system,[6b,c] addition of 2.2 equiv DBU accelerated the dehydrogenation of ^{4Me}BnOH by $[La(L_{QQ})(NO_3)_3]$ with ^{4Me}PhCHO produced in 63 ± 3% yield (^{1}H NMR spectroscopy) in <10 min with completion of the reaction at this point. No detectable quantity of $^{4Me}PhCO_2H$ was produced and only broad, indistinct peaks for L_{QQ} containing product(s) were observed (Figure S29). Performing the reaction on a preparative scale gave pure, black-green $[La(L_{QQ}^{2-})(NO_3)]_2$ in 67% yield. This dimer was also synthesized from $[La(L_{QQ})(NO_3)_3]$ and 2 equiv $[Cp_2Co]$ (91%; Scheme 2). The considerably less basic, and thus more physiologically relevant, 2,6-lutidine could be substituted for DBU ($pK_a \sim 7$ cf. ~12 for DBU).[12] The reaction, while slower, was still much faster (complete in <24 h) than that in the absence of a base, and gave ^{4Me}PhCHO in 37% yield (Table S3). A control reaction of L_{QQ} with 1.2 equiv ^{Me}BnOH and 2.2 equiv DBU produced only trace amounts (<3% yield) of ^{4Me}PhCHO in 30 min (13% after 4 h). $[La(L_{QQ}^{2-})(NO_3)]_2$ is the first structurally characterized metal complex of a reduced quinoline quinone. Notably, Itoh and Fukuzumi assigned the product of the reaction of PQQ-trimethylester (PQQTME), Ca^{2+}, an alcohol and DBU as a

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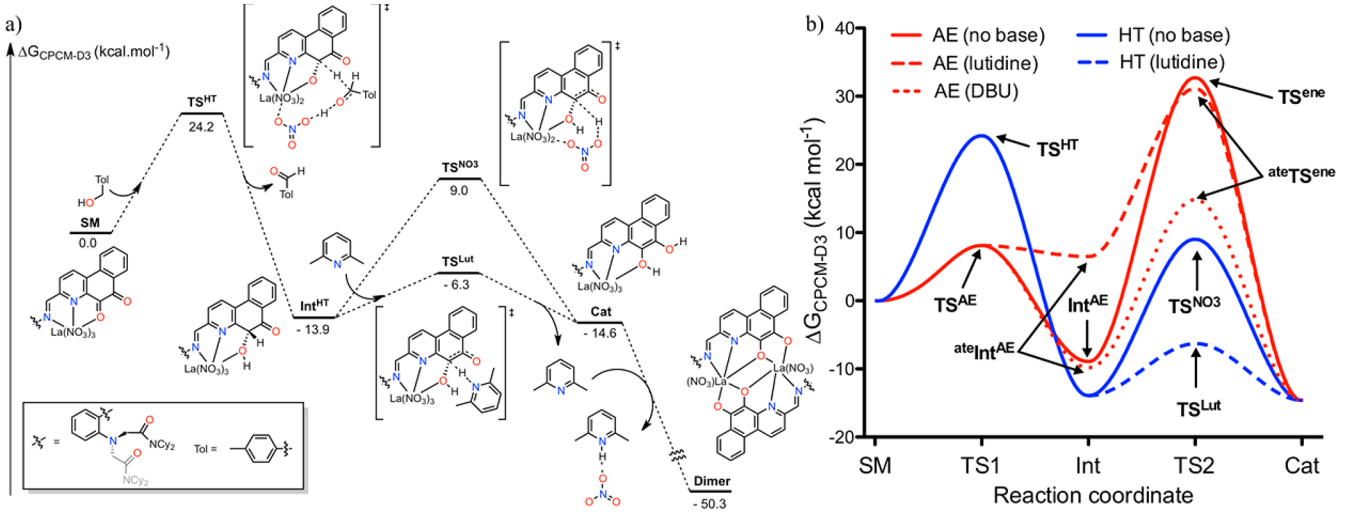

Figure 2. DFT-calculated reaction coordinates for the dehydrogenation of ^{4Me}BnOH by [La(L_{QQ})(NO_3)$_3$]: (a) a 2,6-lutidine-assisted HT mechanism; (b) comparison of the AE (red traces) and HT (blue traces) mechanisms in the absence of base (solid traces) and the influence of DBU (dotted trace) or 2,6-lutidine (dashed traces).

monomeric, singly deprotonated catechol complex,[6b] in contrast to fully deprotonated [La(L_{QQ}^{2-})(NO_3)]$_2$.

We hypothesized that, with a suitable terminal oxidant and base, the dehydrogenation of ^{4Me}BnOH by [La(L_{QQ})(NO_3)$_3$] could be performed catalytically. A mixture of 1 equiv ^{4Me}BnOH, 2 equiv [Fc][PF_6], 2 equiv 2,6-lutidine (as DBU was incompatible with [Fc]$^+$ salts) and [La(L_{QQ})(NO_3)$_3$] (5 mol %) in CD_2Cl_2–CD_3CN (2:1 v/v) was monitored by ^{1}H NMR spectroscopy (Figure S30). In <20 min, characteristic peaks corresponding to ^{4Me}PhCHO were observed. After 21 h, ^{4Me}PhCHO had been produced in 84% yield (~17 turnovers) with 85% of the ^{4Me}BnOH having been consumed, indicating clean conversion. Extending the reaction another 24 h increased the yield of aldehyde to 96%. In the absence of [La(L_{QQ})(NO_3)$_3$], no ^{4Me}PhCHO was produced within 24 h under these conditions. Replacing [La(L_{QQ})(NO_3)$_3$] with 5 mol % [La(THF)$_4$(NO_3)$_3$] or L_{QQ} gave ^{4Me}PhCHO in 5% or 14% yield, respectively, after 21 h. These results show the requirements of both La and the L_{QQ} ligand for catalytic turnover. The dehydrogenation of ~60 mg of ^{4Me}BnOH, catalyzed by [La(L_{QQ})(NO_3)$_3$], was carried out under the above conditions to afford ^{4Me}PhCHO and Fc in 75% and 83% isolated yields, respectively, in 24 h. Itoh and Fukuzumi reported dehydrogenation of ethanol (~15 turnovers in 65 h) by a mixture of [Ca(ClO_4)$_2$], PQQTME, DBU and O_2.[6b] Until our report, theirs was the only nonbiological example of alcohol dehydrogenation catalyzed by a metal complex of a PQQ derivative. Notably, our system does not employ O_2, which may oxidize the aldehyde to give carboxylic acid byproducts.

For further insights into the reactivity and properties of [La(L_{QQ})(NO_3)$_3$], we turned to computations. The gas-phase structures of L_{QQ}, [La(L_{QQ})(NO_3)$_3$], putative [La($L_{QQ}^{\bullet-}$)(NO_3)$_3$] and [La(L_{QQ}^{2-})(NO_3)]$_2$ were optimized by density functional theory (DFT) methods and gave good agreement with XRD metrics (Table S5). All carbonyl IR stretches were well reproduced (Figures S38–40). In addition, a +0.51 V relative stabilization of [La($L_{QQ}^{\bullet-}$)(NO_3)$_3$] cf. $L_{QQ}^{\bullet-}$ was predicted, compared to +0.61 V observed experimentally (Figure S37). Encouraged by the agreement of DFT calculations with experimental data, we examined possible mechanisms for the dehydrogenation of ^{4Me}BnOH by [La(L_{QQ})(NO_3)$_3$]. The catalytic pathway of MDH has been considered to occur through one of two plausible mechanisms: hydride transfer (HT) or addition–elimination (AE).[13] Although the HT mechanism is generally accepted for biological MDH enzymes,[14] recent computational work on Ln-XoxF indicated a possible preference for the AE mechanism.[15]

In the current work, the HT mechanism was considered first (Figures 2a and S47–48). In the first calculated transition state (TS), a benzylic hydride was transferred to the C(2)-QQ carbon atom from ^{4Me}BnOH with concerted alcohol deprotonation by a NO_3^- ligand (**TS^{HT}**, $\Delta G^{\ddagger}$ = 24.2 kcal mol^{-1}). This step afforded ^{4Me}PhCHO, HNO_3 and the hemiacetalate complex (**Int2**). Reprotonation of **Int2** by HNO_3 to the hemiacetal (**Int^{HT}**) was nearly barrier-less. Enolization of **Int^{HT}** was assisted by a NO_3^- ligand to give the catechol complex with an activation barrier of 22.9 kcal mol^{-1} (**TS^{NO3}**). Explicit action of 2,6-lutidine reduced the barrier for enolization by ~15 kcal mol^{-1} (**TS^{Lut}**, $\Delta G^{\ddagger}$ = 7.6 kcal mol^{-1}). Deprotonation of the catechol afforded dimeric [La(L_{QQ}^{2-})(NO_3)]$_2$, which was downhill by ~35 kcal mol^{-1}.

The AE mechanism was also examined (Figures 2b and S45–46). As expected,[6b,c,14b,15] NO_3^--assisted addition of ^{4Me}BnOH at the C(2)-QQ carbon atom to give the hemiketal complex (**Int^{AE}**) had a low barrier of 8.1 kcal mol^{-1} (Figure 2b). The barrier for the subsequent retro-ene step (**TS^{ene}**) to yield the catechol complex (**Cat**) and ^{4Me}PhCHO was ~40 kcal mol^{-1} and base did not facilitate this step. The activation energy for the retro-ene step was lowered (**^{ate}TS^{ene}**, $\Delta G^{\ddagger}$ = 24.5 kcal mol^{-1}) from the deprotonated hemiketalate complex (**^{ate}Int^{AE}**) as similarly calculated by others.[15,16] However, formation of **^{ate}Int^{AE}** over **Int^{AE}** was only favored in the presence of DBU, but not weakly basic 2,6-lutidine (Figure 2b, dashed and dotted lines). Thus, in the presence of DBU, [La(LQQ)(NO_3)$_3$] may oxidize 4MeBnOH by an AE mechanism, as reported for Ca^{2+}-PQQTME complexes.[6b,c]

Overall, our DFT study suggested that for the dehydrogenation of ^{4Me}BnOH by [La(L_{QQ})(NO_3)$_3$]: (i) in the absence of a base, the HT mechanism should be preferred with two free energy barriers of ~24 kcal mol^{-1}, consistent with a slow reaction at r.t. (ii) under our catalytic conditions HT should

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also be favored, as 2,6-lutidine should enhance the rate by facilitating the enolization process (iii) nitrate ligands are important in both mechanisms by acting analogously to the "proton-shuttle" pendant carboxylate in MDH enzymes.[13−15]

We have synthesized a functional model for the lanthanide-dependent XoxF-MDH enzyme. This complex dehydrogenated a benzyl alcohol stoichiometrically and catalytically under neutral and mildly basic conditions. DFT investigations suggested a HT mechanism for these reactions and, by extension, for MDH enzymes. Efforts to expand these studies are underway, for example, by gauging the impact of changing the nitrate coligands and/or the rare-earth cation on the catalytic activity of our model system.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b12318.

Synthetic procedures and spectroscopic data, NMR spectra from reaction mixtures, additional electrochemistry and computational data (PDF)

X-ray crystallography data (CIF)

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Notes

The authors declare no competing financial interest.

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