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Substituted Quinoline Quinones as Surrogates for the PQQ Cofactor: An Electrochemical and Computational Study§

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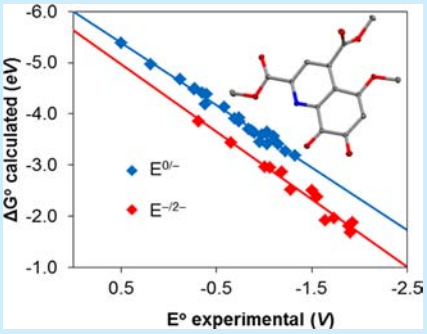
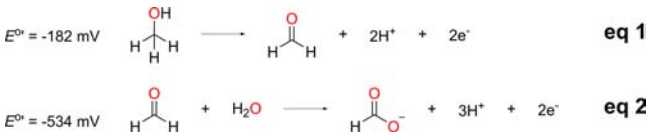
Supporting Information

ABSTRACT: Pyrroloquinoline quinones (PQQ) are important cofactors that shuttle redox equivalents in diverse metalloproteins. Quinoline 7,8-quinones have been synthesized and characterized as surrogates for PQQ to elucidate redox energetics within metalloenzyme active sites. The quinoline 7,8-quinones were accessed using polymer-supported iodoxybenzoic acid and the compounds evaluated using solution electrochemistry. Together with a family of quinones, the products were evaluated computationally and used to generate a predictive correlation between a computed ΔG and the experimental reduction potentials.



Methanol is the second most abundant organic compound in the atmosphere after methane and holds an important position in the carbon cycle.[1] Methanol dehydrogenase (MDH) enzymes are used by some organisms to drive aerobic respiration and provide carbon in different oxidation states for biosynthesis.[2] The first step to using methanol as a fuel or a building block is dehydrogenation to formaldehyde, followed by oxidation to formate (Scheme 1).

Scheme 1



Methanol dehydrogenase enzymes include a pyrroloquinoline quinone, PQQ, cofactor bound to a Ca^{2+} cation in the active site to catalyze the reaction (Scheme 1, eq 1).[3,4] These calcium-dependent enzymes and the PQQ cofactor have been studied *in vitro*, *in silico*, and using model complexes.[5−8]

Recently, a lanthanide-dependent MDH enzyme was discovered that efficiently catalyzes reactions (Scheme 1, eqs 1 and 2) at rates 10^2−10^3-fold higher than their calcium-dependent counterparts.[9,10] Typically, the Lewis acidity of metal centers can be quantified through measurement of electron transfer rate constants using electron paramagnetic resonance, changes in the fluorescence of a coordinated ligand, or reduction potentials of the metal ion.[11,12] Another method for interrogating the Lewis acidity of a redox-inactive metal cation is to measure the redox potentials of a coordinated ligand.[7,13,14] To understand the electronic structure of the active sites in these enzymes, the electrochemical properties of the essential quinone cofactors must be established. To this end, we have synthesized a group of PQQ surrogates and characterized them electrochemically and computationally to establish a predictive correlation of their first and second reduction potentials, along with the potentials of many quinones available in the literature. With this correlation and the surrogates **3a−c** in hand, MDH model complexes can be designed and realized. The Lewis acidity of these complexes can then be determined electrochemically and computationally.[15]

Synthesis of the quinoline quinones **3a−c** (Scheme 2) began with the condensation of substituted 2-aminophenols with dimethyl 2-oxoglutaconate in 1,2-dichloroethane at reflux for 24 h with *p*-toluenesulfonic acid as a catalyst to yield the 8-hydroxyquinolines, **2a−c**.[16,17] The reactions, monitored by LCMS, proceeded in low yields (19−28%) but furnished the precursor compounds (**2a−c**) following purification by column chromatography on silica gel, eluted with hexanes and ethyl acetate.

In pursuit of a R = −Ph 8-hydroxyquinoline, the expected mass was not detected by LCMS. Instead, the only mass observed was for that of the benzoxazinone, **4d**. The isolation of **4d** was attributed primarily to the increased steric bulk of the phenyl substitution at the 4-position of **1d**. The steric encumbrance at the 4-position of the aminophenol evidently favored lactonization, forming **4d**. Following characterization of **4d**, we noticed the related compound **4b** where R = −Me, similarly formed during the synthesis of **2b**. Compound **4b** was also isolated by column chromatography and fully characterized. Attempts to reverse this condensation and generate the desired **2d** were unsuccessful.

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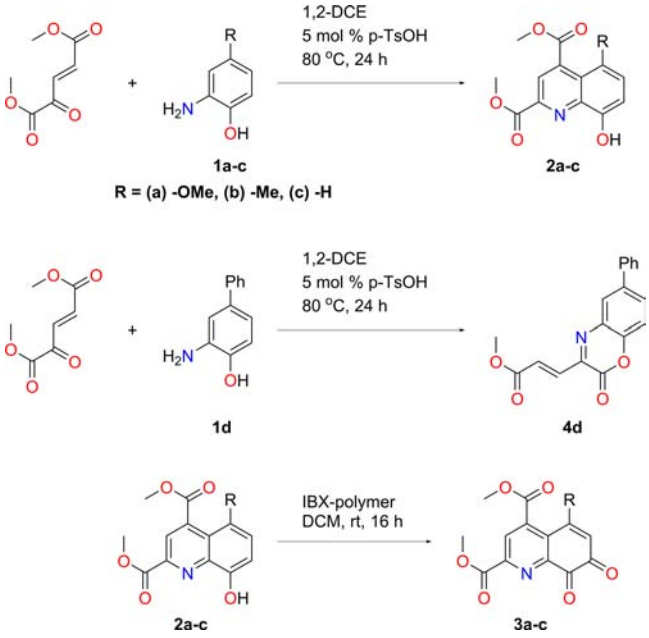
Scheme 2. Synthesis of 2a−c, 3a−c, and 4d



Following their purification, we explored oxidation procedures to convert the precursors **2a−c** to the quinones **3a−c**. Several oxidants were screened, including 2-iodoxybenzoic acid (IBX), Fremy's salt, and CAN, before settling on a polymer-supported IBX derivative.[18,19] Precursors **2a−c**, dissolved in dichloromethane, were agitated with the polymer-supported IBX for 16 h. The IBX polymer was removed by filtration using a medium porosity fritted filter, and the solvent was removed to afford the quinoline quinones **3a−c**. Compounds **3a−c** were isolated in high yields (90−99%). The IBX−polymer was regenerated by agitation with $^{n}Bu_4NHSO_5$ and methanesulfonic acid in DCM for 3 h.[20] The regenerated polymers were used up to four times before depreciation in activity was observed.[19] Compounds **3a−c** were characterized by ^{1}H and ^{13}C NMR, IR and UV−Vis spectroscopy, and electrochemistry.

Compound **3a** was also characterized crystallographically (Figure 1). **3a** was crystallized by slow evaporation of a concentrated $CHCl_3$ solution. This is the first example of a crystallographically characterized neutral quinoline quinone. The only previous structures were reported for sodium or copper salts. The quinone bond lengths of **3a**, C(8)−O(2) 1.2054(15) Å and C(7)−O(1) 1.2217(16) Å, compared well with the bond lengths found in the crystal structure of the doubly deprotonated disodium salt of the parent carboxylate PQQ, which were 1.2051(9) and 1.2047(6) Å, respectively.[21] One difference between **3a** and PQQ was that the C(7)−O(1) bond length in **3a** was almost 0.02 Å longer than that of PQQ. We attributed this difference to electron donation from the methoxy substituent into the π^* of the α,β-unsaturated carbonyl moiety, which lengthened the carbon−oxygen bond.

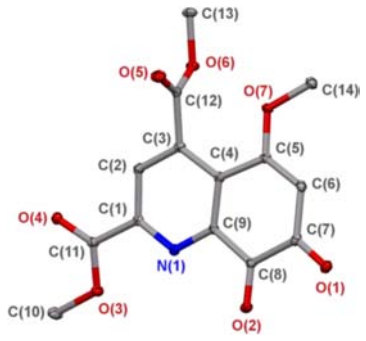


Figure 1. Thermal ellipsoid plot of complex **3a**. Thermal ellipsoids set at 30% probability. Hydrogen atoms were omitted for clarity. Selected bond lengths [Å]: C(8)−O(2) 1.2054(15), C(7)−O(1) 1.2217(16), C(5)−O(7) 1.3388(15). Crystallography details are included in the Supporting Information.[22−26]

We continued the characterization of compounds **3a−c** using density functional theory (DFT) methods in the Gaussian software package.[27] Optimized structures were obtained using the 6-31G* basis set and a CPCM solvent field using acetonitrile as the solvent. Frequency calculations revealed no negative frequencies, indicating that the geometries obtained were energetic minima. The DFT-optimized bond distances and angles for **3a** were consistent with the crystal structure. The experimental quinone bond lengths, C(8)−O(2) 1.2054(15) Å and C(7)−O(1) 1.2217(16) Å, were comparable to the calculated values of 1.2142 and 1.2274 Å, respectively.

IR spectra were collected for compounds **3a−c** using KBr pellets and were also compared to their computed spectra from the DFT-optimized frequency calculations. The positions of the peaks were corrected based on a reported correction for the 6-31G* basis set.[28] The carbonyl stretching frequencies (1820−1650 cm^{-1}) were consistent with experiment. In the spectrum for **3a**, for example, the carbonyl peaks at 1732, 1718, and 1657 cm^{-1} matched well in position and intensity with the calculated carbonyl stretches at 1735, 1731, and 1663 cm^{-1}, respectively (Figure S20). In the spectrum of **3b**, two peaks were observed in the carbonyl region at 1736 and 1678 cm^{-1}. These matched the three calculated peaks at 1733, 1723, and 1676 cm^{-1} (Figure S29). The two calculated peaks at 1733 and 1723 cm^{-1} overlapped in the experimental spectrum, producing the peak observed at 1736 cm^{-1}. In the spectrum of **3c**, two peaks were observed in the carbonyl region at 1732 and 1684 cm^{-1}. These matched the three calculated peaks at 1733, 1713, and 1684 cm^{-1} (Figure S36). For **3c**, the overlapping of two peaks contributed to the large peak at 1732 cm^{-1} in the experiment. We expect these carbonyl stretches to be useful spectroscopic markers for exploring the use of **3a−c** as ligands.

For the purpose of predicting the redox energetics and associated electrochemistry of the quinoline quinones, we selected quinones from the literature that had been electrochemically characterized.[29−31] Gillmore and co-workers previously established the utility of DFT for assessing redox energetics in the first reduction of organic molecules.[31] The quinones we selected and synthesized (Figure 2a,b) were all structurally optimized in their neutral, radical anionic, and dianionic states using a series of DFT calculations. All of the structures converged and were confirmed to have no negative frequencies. The total thermal free energy values were then extracted from the results of their frequency calculations. The differences in energy (ΔG) from neutral quinone to semiquinone were calculated and plotted versus the experimental $E_{1/2}$ values reported for their solution electrochemistry.

A linear positive correlation between experimental $E_{1/2}$ and DFT-computed results was evident with an R^2 value of 0.9839 (Figure 2c). This approach provided a method to predict reduction potentials from DFT-optimized structures. The same procedure was then used to correlate the free energy differences between the radical anion and the dianion with the second

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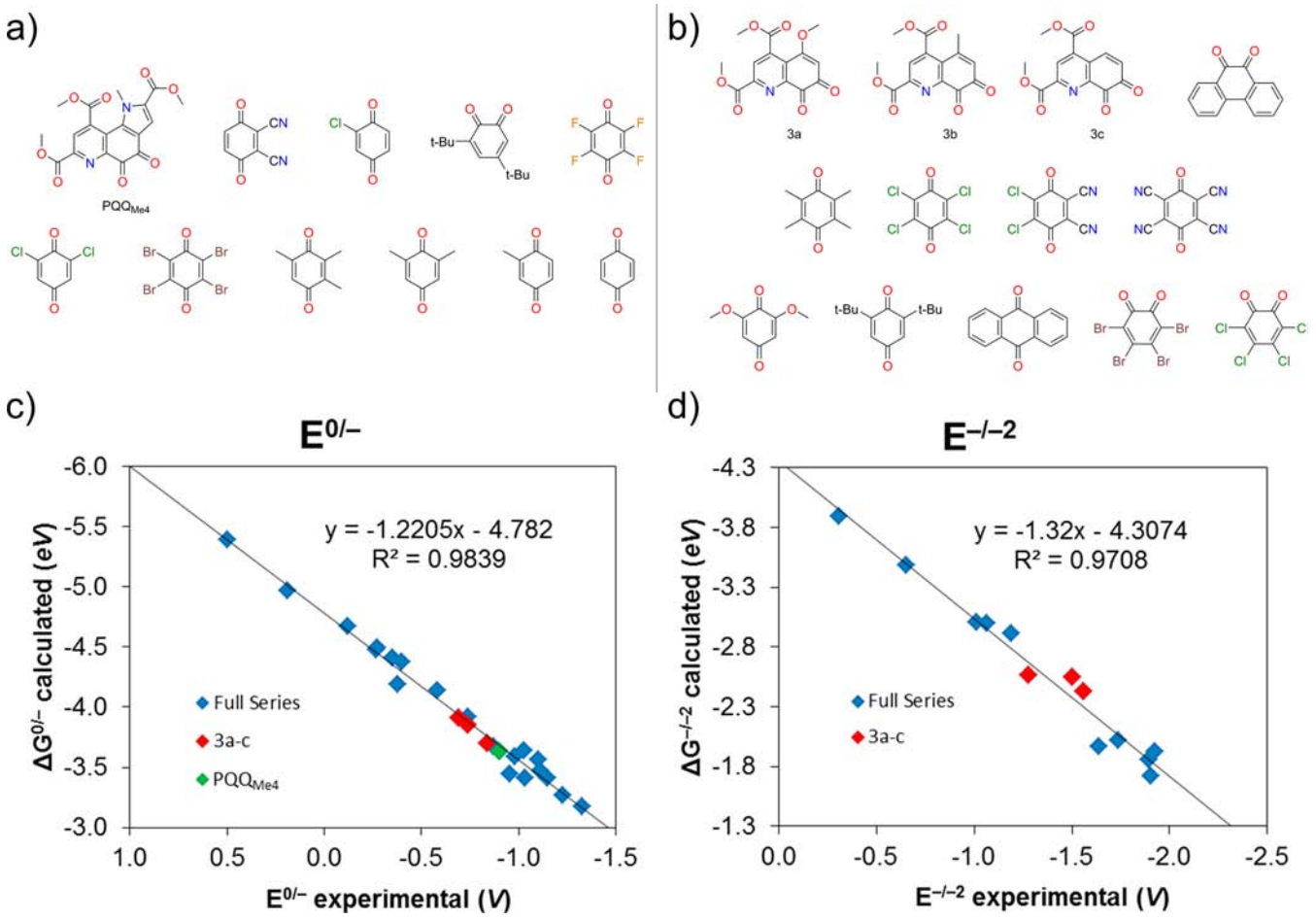

Figure 2. (a) Structures of quinones with first and second reduction potentials experimentally determined. (b) Structures of quinones with only first reduction potentials experimentally determined. (c) Observed potential versus computed free energy difference for the first reduction. (d) Observed potential versus computed free energy difference for the second reduction.

reduction potential, affording a linear correlation with R^2 = 0.9708 (Figure 2d). The predictive power of the quinone correlation was further evaluated using the mean absolute deviation (MAD).[32] The MAD for the first reduction potential correlation was 46 mV, and the MAD for the second reduction potential correlation was 68 mV. We attributed the larger deviation in the second correlation to a larger number of first reduction potentials available in the literature compared to second reduction potentials.

Recording the cyclic voltammogram of **3a** in acetonitrile with $[Pr_4N][BAr^F{}_4]$ as the supporting electrolyte,[33] three reduction features were observed at potentials less than the open circuit potential, at $E_{1/2}$ = −0.84, −1.56, and −2.07 V versus Fc/Fc^+. Scan rate dependences of these features were measured, and they showed the expected linear relation to $\nu^{1/2}$. Randles-Sevcik plots depicting this relationship are included in the Supporting Information. We attributed the reductions to the first and second reduction of the quinone, followed by a reduction centered primarily on the pyridine ring and the ester functional group in the 4-position. Assignments of the waves were supported by visualizing our DFT results using the Chemcraft software package.[34] These visualizations showed the associated HOMO character for each redox form. The calculated values, $E_{1/2}$ = −0.88 and −1.46 V versus Fc/Fc^+, for the first and second reduction potential matched reasonably well with the experimental reduction potentials. The values for **3b** and **3c** were also determined and are depicted in Figure 2. Finally, we found the first reduction potential of a PQQ derivative isolated in the literature, PQQ_{Me4}.[7] The first reduction potential was measured to be −0.90 V, and our prediction placed the potential at −0.94 V, within the MAD for that correlation. This result demonstrated the utility of our correlation for complex quinones. The second reduction potential for PQQ_{Me4} was not available.

In conclusion, we have synthesized a series of 5-substituted quinoline 7,8-quinones, **3a**−**c**, and these compounds were characterized electrochemically and computationally. Their positions were determined among a larger set of *o*- and *p*-quinones in a correlation of their computed ΔG versus their experimental reduction potentials. Using these correlations allows us to predict the electrochemical properties of theoretical PQQ analogues beyond those synthesized in this work. The synthetic scheme presented here allows for a variety of substituted quinoline quinones to be isolated. Compounds **3a**−**c** are currently being investigated as ligands for lanthanide cations, and the resulting compounds will be used as model complexes to investigate the mechanism of methanol dehydrogenation in lanthanide-based MDH model complexes. The flexible and predictive strategy presented herein allows for fine control of the electronic properties of the quinone cofactors to be used in future studies.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details, NMR spectra, IR spectra, UV−vis spectra, full electrochemical data, DFT-optimized coordinates, X-ray structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

§This paper is dedicated to Professor Madeleine M. Joullié, University of Pennsylvania, on the occasion of her birthday.

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