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OXIDATION OF PRIMARY ALIPHATIC AMINES CATALYZED BY AN ELECTROGENERATED QUINONOID SPECIES: A SMALL MOLECULE MIMIC OF AMINE OXIDASES

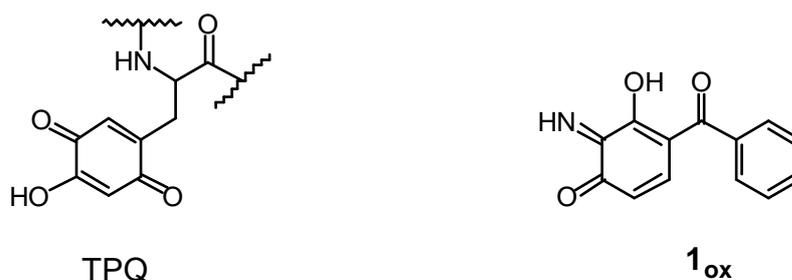
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ABSTRACT

High catalytic performance of the redox mediator 3,4-iminoquinone $\mathbf{1}_{\text{ox}}$ is observed under metal-free conditions in the chemoselective indirect electrochemical oxidation of unactivated primary aliphatic amines to the corresponding alkyimines.

INTRODUCTION

The copper amine oxidases are ubiquitous quinoproteins which catalyze the two-electron oxidative deamination of a primary amine to produce the corresponding aldehyde and ammonia, with subsequent two-electron reduction of dioxygen to hydrogen peroxide (1). To carry out this reaction, these enzymes contain two cofactors, an organic cofactor, topaquinoxinone (TPQ) and a cupric ion. It is well established that TPQ catalyzes the conversion of an amine substrate into an aldehyde through a pyridoxal-like transamination mechanism, which results in the reduction of TPQ to an aminoquinol form. Although there is no question regarding the crucial role of copper in the biogenesis of TPQ, the role of the copper cofactor during amine oxidation is, however, less well understood. Recent intensive biochemical studies are fairly consistent with a passive role of copper in the catalyzed amine oxidation process (2-4). A few years ago, we have shown that electrogenerated 3,4-iminoquinone $\mathbf{1}_{\text{ox}}$ acts as an efficient catalyst for the autorecycling oxidation of benzylamine through the transamination process reported for amine oxidase cofactors (5). The catalytic cycle produced the reduced catalyst $\mathbf{1}_{\text{red}}$ and N-benzylidene-benzylamine as the product of benzylamine oxidation in 3200% yield (based on the initial concentration of $\mathbf{1}_{\text{red}}$). In contrast to other existing amine oxidase model cofactors, $\mathbf{1}_{\text{ox}}$ was also very active toward aliphatic amines. Herein, we report for the first time the catalytic oxidation of primary aliphatic amines by a small-molecule enzyme mimic under metal-free conditions.



Scheme 1. Topaquinoxinone (TPQ) and 3,4-iminoquinone model cofactor $\mathbf{1}_{\text{ox}}$.

EXPERIMENTAL

General procedure - Controlled-potential electrolysis was carried out in a cylindrical, three-electrode divided cell. In the main compartment, a platinum grid (area = 60 cm²) served as the anode. A platinum sheet was placed in the concentric cathodic compartment, which was separated from the main compartment with a glass frit. The reference electrode was an aqueous saturated calomel electrode (SCE), which was isolated from the bulk solution in a glass tube with a fine-porosity frit. The electrolyte solution (0.04 mol.L⁻¹ lithium perchlorate in methanol) was poured into the anodic and the cathodic compartments, as well as into the glass tube that contained the SCE electrode. 3,4-Aminophenol **1_{red}** (0.1 mmol) and an excess of primary aliphatic amine (5 mmol) were added to the solution in the main compartment (250 mL), and the resulting solution was then oxidized at + 600 mV vs SCE, under nitrogen, at room temperature (initial current 30-40 mA).

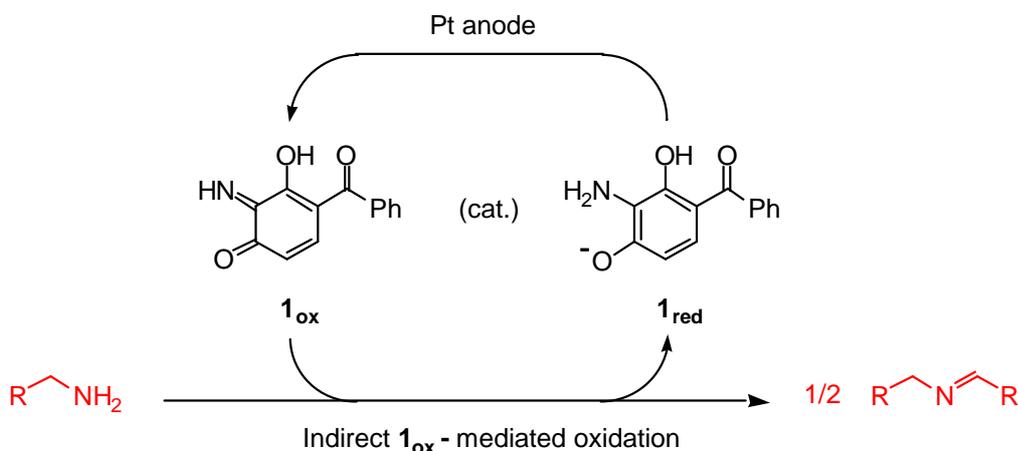
Isolation of aldehyde 2,4-dinitrophenylhydrazine (DNPH) - After exhaustive electrolysis (6-10h, n = 8-56, n being the total number of electrons transferred per molecule of **1_{red}** in the catalytic process), that is, when a negligible value of the current was recorded (0.5-1.0 mA), the solution was worked up by addition of 2.5 mmol of 2,4-dinitrophenylhydrazine reagent (in 5 mL of pure H₂SO₄, 15 mL of EtOH and 5 mL of water), because 5 mmol of primary amine gave 2.5 mmol of alkyimine (scheme 2). After 1h, the resulting solution was concentrated to 40 mL. The solid was collected by filtration, washed with water and dried in a vacuum desiccator. The identity and purity of DNPH was confirmed by TLC and ¹H NMR spectroscopy, after comparison with an authentic sample. In the case of n-hexylamine or phenylpropylamine, the solid was purified by chromatography on silica gel to separate DNPH from 1,2-bis-DNPH.

Isolation of 1,4-benzoxazines 2 and 3 - After exhaustive electrolysis (6h, n = 9 or 10), the electrolysis solution was poured into an acetic acid buffered aqueous solution of pH 4.8 (1 mol L⁻¹, 50 mL). The resulting hydroalcoholic solution was concentrated to remove methanol. The yellow solid, identified as the 1,4-benzoxazine derivative (6), was collected by filtration, washed with water, and dried in a vacuum desiccator.

RESULTS AND DISCUSSION

The cyclic voltammogram of 3,4-aminophenol **1_{red}**, recorded under our experimental conditions (see Experimental), showed an oxidation peak Pa at 0 mV, characteristic of the two-electron oxidation of **1_{red}** to **1_{ox}**, the sweep rate being 0.5 V s⁻¹. When the controlled potential E of the platinum anode was fixed at + 600 mV (a high potential value was chosen because a shift of the peak Pa to +500 mV was observed in the course of the electrolysis, when the amine concentration was no more sufficient to ionize the 4-hydroxyl group of **1_{red}**), the anodic current remained unchanged for a long time, consistent with steady-state catalytic behaviour. Accordingly, a high value (up to 56) was found for n. These results indicated that the **1_{red}**/**1_{ox}** system behaved as a redox-mediator for the indirect electrochemical oxidation of unactivated primary aliphatic amines to the corresponding alkyimines (Scheme 2), according to the transamination mechanism previously reported (5). After exhaustive electrolysis, the catalyst **1_{ox}** was lost irreversibly as corroborated by the anodic current which remained negligible upon further addition of amine substrate. Unstable alkyimine was isolated in terms of the corresponding DNPH obtained upon workup of the oxidized solution with 2,4-dinitrophenylhydrazine (see Experimental). Control experiments indicated that the

amount of aldehyde produced either from simple autoxidation or from electrochemical oxidation of the starting amine in the absence of catalyst was negligible.

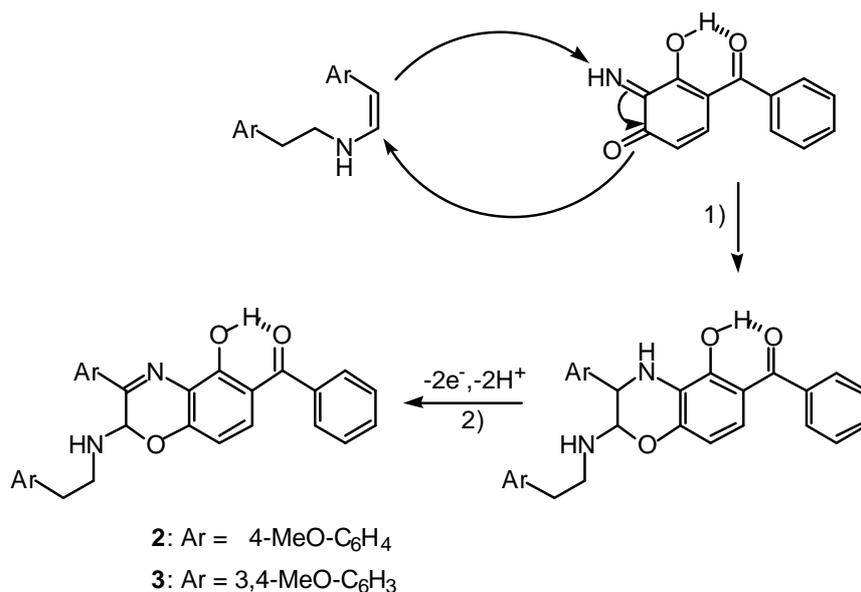


Scheme 2. Catalytic oxidation of primary aliphatic amines mediated by electrogenerated 3,4-iminoquinone model cofactor $\mathbf{1_{ox}}$.

From our results, it appeared that the most efficient substrates for $\mathbf{1_{ox}}$ were alkyl primary amines ($R = \text{cyclohexyl}$, cyclopropyl , or $R = R'-\text{CH}_2$ with $R' = \text{Bu}^t$, Pr^i , OH) with yields of isolated DNPH ranging from 1000 to 2300% (relative to the mediator). With *n*-hexylamine, although a high value of 48 was found for *n*, the catalytic oxidation of longer chain more hydrophobic amine produced DNPH in only 305% yield, along with 255% of a second product identified as the osazone (1,2-*bis*-DNPH). Interestingly, as for the enzymes themselves, α -branched amines like cyclohexylamine were found to be poor substrates for the model catalyst $\mathbf{1_{ox}}$ (110% of DNPH), whereas secondary amines were not reactive at all.

Primary amines bearing aromatic rings also underwent deamination, though the turnover was much lower on account of a more rapid deterioration of the catalyst. With phenylpropylamine ($R = \text{Ph}-\text{CH}_2-\text{CH}_2$), a value of 38 was found for *n*. Similarly to *n*-hexylamine, both DNPH (650%) and 1,2-*bis*-DNPH (100%) could be isolated at the end of the catalytic process. Further investigations would be necessary to justify the formation of the osazone which seems favored when starting amines are not sterically encumbered by β and γ branching.

With ring-substituted phenylethylamines ($R = \text{Ar}-\text{CH}_2$), the catalytic process ceased after a few turnovers ($n = 9$ or 10). Close inspection of the exhaustively oxidized solution revealed that electrogenerated 3,4-iminoquinone $\mathbf{1_{ox}}$ was trapped with the tautomeric enamine form of the alkylimine extruded during the catalytic process (Scheme 2) through an inverse-electron-demand Diels-Alder reaction (7), affording unstable 1,4-benzoxazine derivatives (step 1, Scheme 3). However, these compounds could be isolated as stable products **2** and **3**, in 50 and 65% yields respectively, after a subsequent two-electron oxidation reaction (step 2). Interestingly, this multi-step one-pot electrochemical procedure could lead to novel neuroprotective agents, due to the structural similarity of **2** and **3** with earlier reported 1,4-benzoxazine derivatives (8).



Scheme 3. Inactivation of model cofactor **1_{ox}** by ring-substituted phenylethylamine substrates, leading to 1,4-benzoxazine derivatives **2** and **3**.

Finally, we have demonstrated for the first time that unactivated primary aliphatic amines can be efficiently oxidized by a synthetic model cofactor of amine oxidases, under metal-free conditions. The catalyst **1_{ox}** exhibits the same substrate specificity than the copper amine oxidases themselves, that is, poor reactivity with α -branched primary amines and no reactivity toward secondary amines. The reaction displays two features that are most often associated with enzymatic systems: a) the reaction is likely enhanced through the participation of neighboring substituents, as they prevented the competing formation of Michael adducts (here, the benzoyl and 2-hydroxyl groups); b) the presence of an active hydroxyl proton very probably constitutes an essential component of the catalytic activity (here, 2-hydroxyl proton, analogous to that of TPQ). We are currently conducting further analogs development to confirm the substantial role of the 2-hydroxyl group to convert a catalytic inert species into a highly effective enzymatic prosthetic group.

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