

Letter

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Electrochemically Mediated Reduction of Nitrosamines by Hemin-Functionalized Redox Electrodes

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Supporting Information

ABSTRACT: Nitrosamines are a major class of contaminants of emerging concern (CECs) that are toxic, present at trace levels in aqueous environments, and challenging to destroy due to their chemical stability. We report novel redox electrodes based on hemin-functionalized carbon nanotubes showing high electrocatalytic activity for nitrosamine reduction at low potentials (-0.5 V vs Ag/AgCl, or -0.27 vs SHE) and with turnover numbers of greater than 700. The redox electrodes were tested under a range of electrolyte and pH conditions with demonstrated high conversion of nitrosamines at high reaction rates, even at ppb levels in secondary effluent from a wastewater treatment plant. We propose that the pathway for nitrosamine reduction involves a proton-mediated conversion of the nitroso group to hydrazines and secondary amines. These high-performance biomimetic electrocatalysts for nitrosamine reduction are based on complexes containing earth-abundant metals, and potentially, have broad applications in environmental remediation, water treatment, and industrial organo-electrochemical processes.

INTRODUCTION

The development of novel, cost-efficient water treatment methods is one of the major science and engineering challenges of the 21st century.¹ In particular, there is urgent need for the discovery of effective chemical strategies to address contaminants of emerging concern (CECs), which include organic pollutants of high toxicity, global aquatic distribution, and environmental persistence in ultra-dilute concentrations.^{2,3} *N*-nitrosamines, CECs that require immediate attention due to their potent carcinogenicity, are currently under direct monitoring by the Environmental Protection Agency (EPA).^{4,5} *N*-Nitrosamines can be found in food derivatives, pesticides, and tobacco-related products;⁶ they are also side-products of various industrial chemical processes and are often released without treatment into public waters.⁷ In addition, nitrosamines are disinfection byproducts due to their significant formation potential through various precursors available in aquatic envi-

ronments.⁸⁻¹⁰ Once formed, nitrosamines are chemically stable and difficult to remove by conventional methods, which in general, lack chemical selectivity and are energetically costly and cumbersome to implement.^{11, 12}

Electrochemical treatment processes have been touted as an ecofriendly alternative to conventional methods due to their low energy input and low waste output.¹³⁻¹⁶ For many organic transformations, however, their use is still limited due to the lack of efficient electrocatalysts. Conductive interfaces have been reported to be effective for various organic reductions, including for nitrosamines, but these are often operated under large voltages (up to 4 V vs SHE).^{17,18} Many of these chemical transformation catalysts are also based on expensive noble metals, and the fundamental challenge thus lies in finding a high-performance and cost-efficient approach to enable electrochemical nitrosamine degradation under low potentials. In this work, we relied on complexes with an earth-abundant metal, iron, with specific redox-activity as our prime basis for electroreductions due to their tunable and chemically-selective electron-transfer processes.^{19,20} Recently, iron-based metallocene redox electrodes have been shown to be highly efficient platforms for recognition and binding of a series of organic CECs.^{21,22}

Hemin, or iron(III)-protoporphyrin IX, a cofactor in many enzyme systems, is a powerful redox-active moiety in its own right. It has been used as an electrocatalyst in a wide range of reactions including O₂^{23,24} and nitric oxide reductions,²⁵ and as an agent in atom-transfer polymerization.²⁶ Hemin's single molecule electron transfer process has been studied in depth,²⁷ and its biomimetic properties have been compared to those of naturally occurring peroxidase enzymes.²⁸ Interestingly, the biological damage caused by nitrosamines occurs when they interact with the heme active site of cytochrome P450,²⁹ through a direct coordination of the nitrosamine functional group with the iron in the heme.³⁰ This naturally-occurring binding affinity, aided by the intrinsic electro-responsive properties of the heme group, has spurred our interest in the use of this metal complex as a heterogeneous electrocatalyst for water purification and environmental remediation. Herein, we

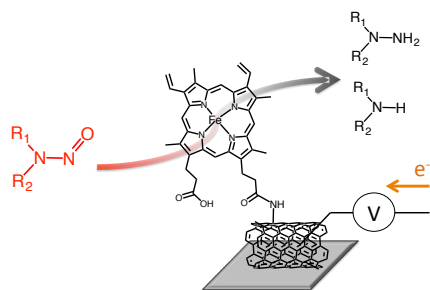


Figure 1. Illustrative scheme of hemin-catalyzed electro-reduction of nitrosamines

report fabrication of novel hemin-functionalized electrodes prepared by covalent attachment of the metalloporphyrin onto amino-functionalized multi-walled carbon nanotubes (NH₂-MWCNTs, **Figure 1**) for the electro-reduction of aqueous nitrosamines, *N*-nitroso-dimethylamine (NDMA) and *N*-nitrosopyrrolidine (NPYR), as well as tobacco-specific nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*-nitrosornicotine (NNN).

MATERIALS AND METHODS

Materials. Ferritroporphyrin IX chloride (hemin from bovine, ≥90%), carbon nanotubes (multi-walled, outer diameter 6-9 nm, length 5 μm, >95% carbon), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (crystalline, 99%, EDAC), (±)-nicotine (≥99% by TLC), *N*'-nitrosornicotine (analytical standard, NNN), 4-(methylnitrosoamino)-1-(3-pyridinyl)-1-butanone (analytical standard, NNK) were all obtained from Sigma-Aldrich Chemical Co. Amino functionalized multi walled carbon nanotubes (outer diameter, < 20 nm; inside diameter, 4 nm; ash, 0 wt%; purity: >99 wt%; CNT-NH₂) were obtained from Cheap Tubes, Inc. (Cambridgeport, VT). Toray paper (carbon fiber composite carbon paper) was obtained from Electrochem Inc. (Woburn, MA).

Synthesis of hemin-CNT conjugate. Hemin (100 mg) was dissolved in 20 mM aqueous NaOH (30 mL) to result in solution A. EDAC (400 mg) was dissolved in phosphate-buffered saline diluted 10-fold by deionized water (pH 7.4, 20 mL) to result in solution B. Amino-functionalized nanotubes (NH₂-CNT) (100 mg) were suspended in phosphate-buffered saline diluted 10-fold by deionized water (pH 7.4) and the suspension was sonicated in an ice-cold bath for 15 min. The suspension was then mixed with solution B; this suspension was subsequently added to solution A. The resulting black suspension was shaken for 8 h at room temperature and dialyzed against excess deionized water (membrane MWCO, 12-14 kDa). The suspension was then centrifuged at 9,000 rpm for 5 min and particles were separated from the supernatant, resuspended in deionized water with sonication and again separated by centrifugation. The process of washing was repeated 3 times. The resulting wet CNT-hemin material was snap-frozen in liquid nitrogen and lyophilized to dryness. Iron content in the CNT-hemin conjugate was measured to be 3.52, 3.83 and 3.74% (average 3.7% wt). This

number yields an estimate of the efficiency of hemin attachment of approximately 90%.

Working Electrode Preparation. The working electrodes were prepared from 2 x 1 cm swatches of Toray paper connected with conductive copper tape and wire by soldering. The hemin-CNT electrodes were prepared by drop casting. A stock suspension of hemin-CNT (80 mg in 10 mL anhydrous chloroform) was sonicated for 15 min in icy water to optimize the dispersion. Then 50 μL of the resulting suspension were drop-cast onto the Toray paper part of the working electrode, and left to dry at 25°C until constant weight. The iron content on the electrodes was measured by ICP-MS, following nitric acid digestion, on an Agilent 7500 ICP-MS, according to EPA Method 6020A.

Cyclic voltammetry (CV) and chronoamperometric measurements were performed with a VersaSTAT 3 potentiostat (Princeton Applied Research, Oak Ridge, TN) using a three-electrode electrolyzer (microcell assembly MF 1065, Bioanalytical Systems, Inc., West Lafayette, IN) consisting of a working electrode (above), a reference Ag/AgCl and a platinum wire auxiliary electrode. The electrolyte concentration and nature changed depending on the measurement, with ionic strengths ranging from 10 mM to 100 mM. Measured concentrations of NDMA, NPYR, NNK, and NNN were used in the electrolyte solutions for testing. For NMR assays in acidic experiments, deuterated hydrochloric acid (DCl) in deuterium oxide (D₂O, pD ~ 1) was used. Apart from cyclic voltammetry, during which the cell was purged with nitrogen flow, all electroreduction measurements were carried out under naturally aerated conditions at 25°C. A working volume of 5 mL was used for most tests, with 10 mL being used for 10 ppb and 100 ppb nitrosamine electro-reductions. Details of nitrosamine and product analysis are reported in the associated supporting information. For testing under realistic conditions, secondary wastewater effluent was collected as grab samples from the Deer Island Sewage Treatment Plant (Winthrop, MA) in February 2017.

RESULTS AND DISCUSSION

Materials Characterization

The immobilization of hemin on carbon surfaces through pi-pi interactions has been reported,²⁸ but as observed in our current electrocatalysis investigation, such simple adsorption does not enable stable functioning of the heterogeneous electrodes. Thus, we prepared hemin-functionalized redox electrodes via carbodiimide-activated conjugation of the carboxylic groups of hemin with amino groups tethered to the surfaces of the MWCNTs (NH₂-CNT) (**Figure 2a**). The resulting hemin-CNT conjugates were suspended in chloroform and then drop-cast onto Teflon-coated carbon paper.²¹ Elemental analysis for iron (total measured content, ~3.5 wt%) indicated the conjugation of hemin to the CNTs was effective.

High-resolution scanning electron microscopy (HR-SEM) of the electrode surface showed a hierarchical

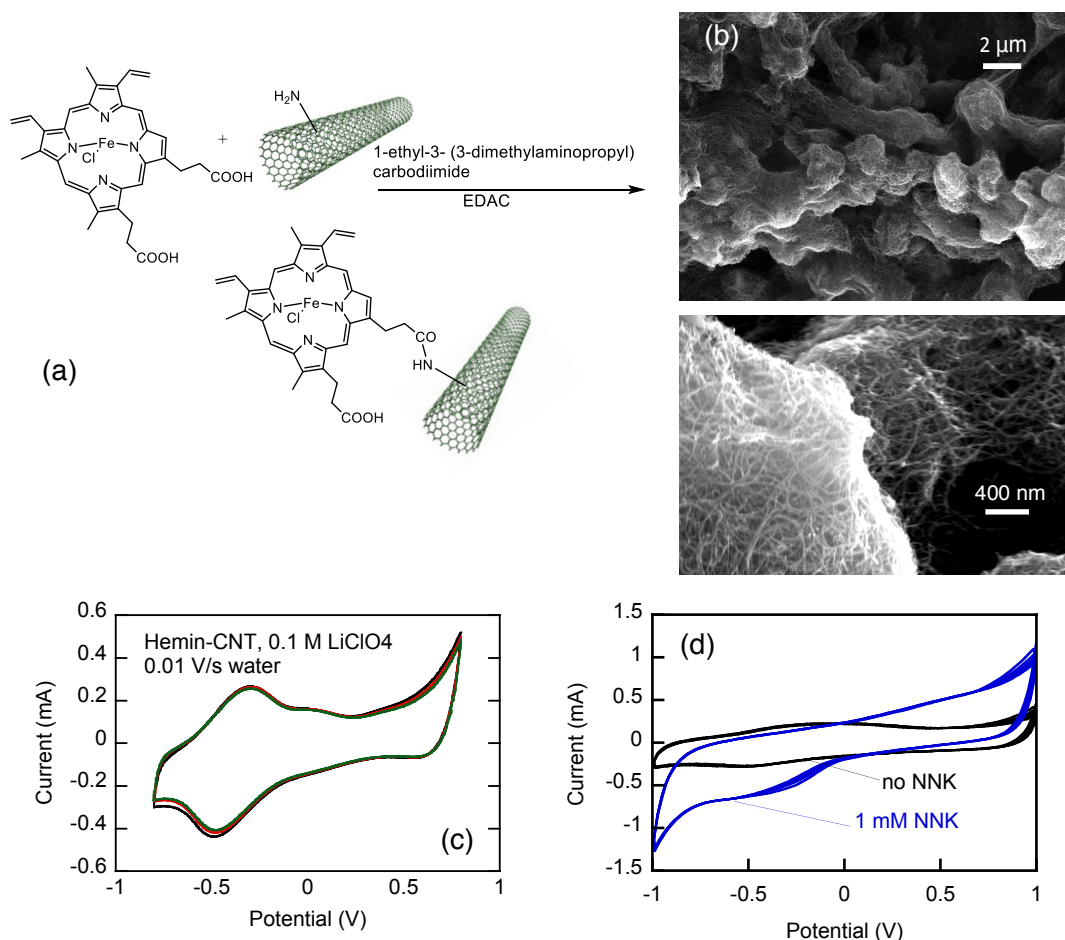


Figure 2. (a) Functionalization procedure for creating **hemin-CNT** electrodes. (b) High-resolution SEM of the electrode surface. (c) Cyclic voltammetry of hemin-CNT at 0.01 V/s (reference Ag/AgCl). (d) Comparison of CV of hemin-CNT with and without 1 mM NNK, in 100 mM LiClO₄ solution at pH 1. Multiple-scans are shown.

porous structure (see **Figure 2b**), with large interconnected pores allowing high accessibility of the substrate to ensure contact with the redox-moieties. The nodules in the top SEM image are seen in the lower SEM image to be composed of a matrix of coated CNTs. A standard 3-electrode setup was utilized for all electrochemical studies, with a Ag/AgCl reference and a Pt counter electrode. The cell was purged by nitrogen under stirring at 240 rpm. The working hemin-CNT electrode was cycled for >100 cycles by CV at 0.01 V/s in 100 mM LiClO₄ with no significant loss of charge (**Figure 2c**), indicating that the heterogeneous conjugation was successful. The clear reversible peaks at -0.5 V vs Ag/AgCl correspond to the Fe(III)/Fe(II) hemin couple. The addition of 1 mM NNK to the electrolyte solution resulted in a significant increase in the magnitude of the electrochemical reduction peak current, evident in **Figure 2d**, consistent with redox-mediation of nitrosamine destruction.

Electrochemical studies

Electroreduction and potential effects. Chronoamperometric destruction of nitrosamines was carried out under a variety of current-voltage, pH, and electrolyte concentrations

with both CNT and hemin-NH₂-MWCNT electrodes; both electrodes were loaded with equivalent charges. The electroreduction for nitrosamine degradation was carried out at room temperature under aerated conditions. First, a series of amperometric reductions was carried out at 0, -0.5, -1, and -1.5 V (vs Ag/AgCl) to evaluate the electrochemical potentials required for effective nitrosamine degradation under acidic conditions in 100 mM LiClO₄ (pH~1) at 100 μM concentrations of the substrate (**Figure 3** and **Figure S10**). NDMA and NPYR were selected as representative EPA-monitored pollutants^{4,7, 31} while NNK is a prominent tobacco-specific nitrosamine.⁶ The solutions were analyzed for nitrosamines and secondary amines by liquid-liquid extraction of 2 mL aliquots of samples in dichloromethane as described elsewhere.³² Notably, nitrosamines were observed to be completely degraded (below detection limits) on the hemin-functionalized and pristine CNT-modified electrodes at high potentials of -1.5 V. However, the conductive carbon surface was found to be a poor candidate for the conversion at potentials lower than -1 V by magnitude. Hemin-CNT, on the other hand, showed significant nitrosamine conversion (~60%) at -0.5 V (vs Ag/AgCl) with current densities up to 1 A/m². For NPYR, up to 90%

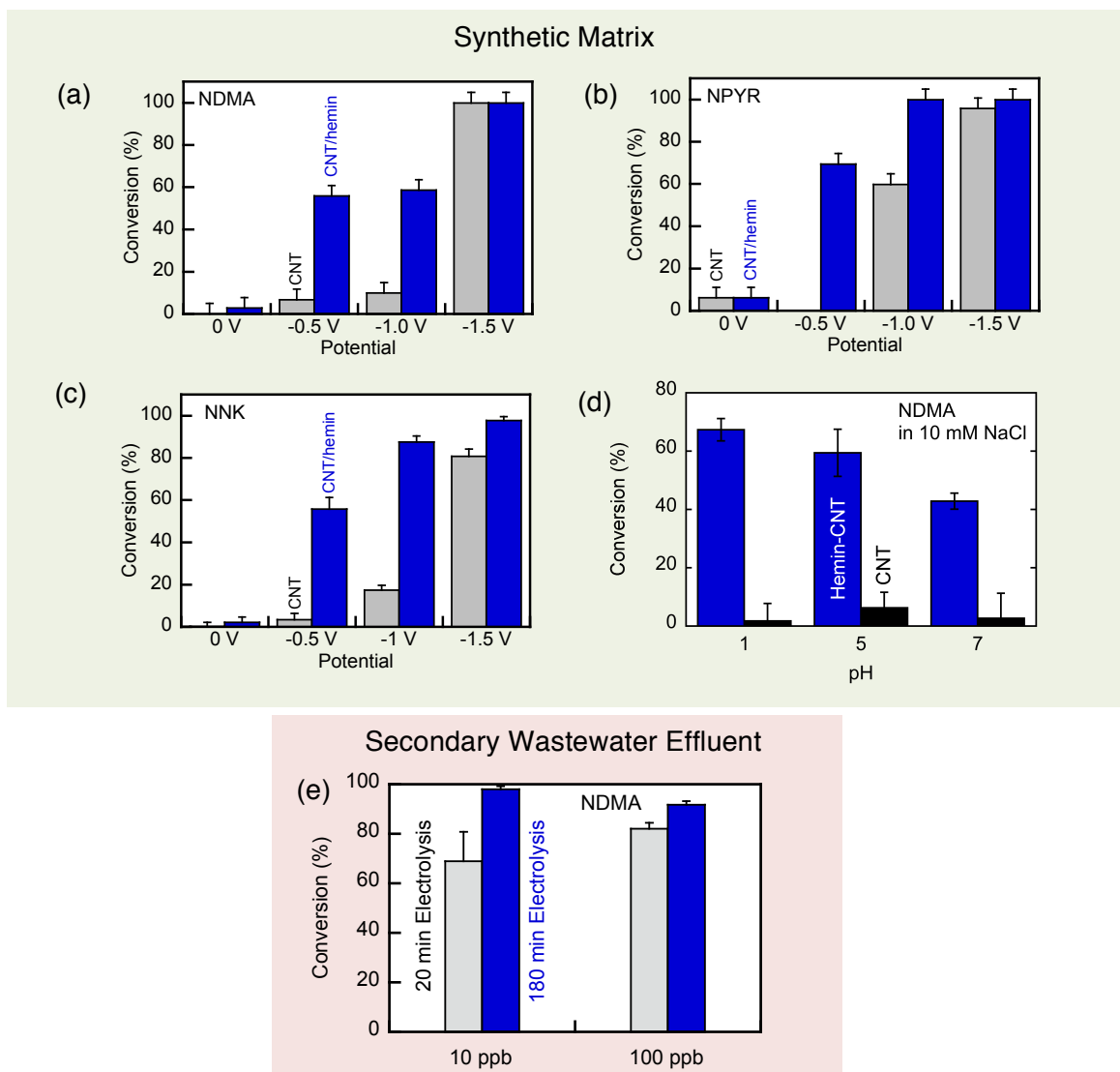


Figure 3. Electrochemical potential-mediated destruction at 100 μM of (a) NDMA, (b) NPYR, (c) NNK for conductive CNT and hemin-CNT electrodes, in 100 mM LiClO_4 at $\text{pH}=1.5$. (d) Electroreduction of NDMA at 100 μM at a constant electrochemical potential of -0.5 V, in 10 mM NaCl under different pH. All these conversions were measured at the end of 20 min electrolysis runs. (e) Decomposition of NDMA at 10 $\mu\text{g/L}$ and 100 $\mu\text{g/L}$ initial concentrations in wastewater matrix (secondary effluent) with no chemical additives or added electrolytes, at two different time scales.

conversion was achieved at -1 V. These results are consistent with cyclic voltammetry studies (Figures S11-12), where large increases in current density were observed with hemin-CNT electrodes upon addition of NDMA, which is attributed to redox-mediated electrochemical reduction. In contrast, there was only a small relative increase in current density with CNT electrodes. Time-dependent studies of the electrochemical reduction showed that the kinetics of NDMA and NPYR destruction were close, with NPYR degrading slightly faster (see Supporting Information).

To demonstrate the catalytic nature of the hemin-CNT electrode and its stability, 15 mM NDMA solution was electroreduced at the hemin-CNT electrode (~ 0.1 μmol hemin loaded) at -0.5 V. A catalytic turnover number

(TON) of ~ 700 was observed with close to 99% conversion, limited only by the substrate availability. Importantly, in the control experiments conducted under acidic conditions in the presence of either CNT or hemin-CNT, but without electrochemical potential, no degradation of nitrosamines was observed on immersion of the electrodes in nitrosamine solution for over 16 h.

Electrolyte and pH effects. Electrochemical destruction of the nitrosamines was also carried out at pH values of 1, 5, and 7 in 10 mM sodium chloride (NaCl). Significantly greater catalytic activity towards NDMA ($\sim 60\%$ conversion after 20 min) was observed with hemin than with CNT, with the acidic solutions being more effective (Figure 3d); over 40% conversion can still be seen at higher pH 7, however. At $\text{pH}=7$ and 10 mM NaCl, the Far-

adaic efficiency of our system towards NDMA destruction can be up to 43% for full degradation to primary amines by assuming a 4e⁻ reduction process. Under acidic tests, this efficiency is correspondingly lower due to the relatively high concentration of protons promoting H₂ evolution. More importantly, under all conditions, both neutral and acidic, if given sufficient time, we were able to destroy the nitrosamines completely (e.g., NNK concentration was lowered from 0.2 g/L to below the sensitivity level of our methods of approximately 1 ng/g, or sub-ppb, after 20 min of electroreduction).

Secondary Wastewater Effluent. The practical applicability of our electrochemical systems was tested on a secondary effluent from a local wastewater treatment plant (Deer Island MWRA, MA), with NDMA added at 10 µg/L (10 ppb) and 100 µg/L (100 ppb) levels to simulate real conditions (pH~6.9, other effluent parameters are given in the discharge monitoring report by Deer Island.³³) No further modification of the water sample was made, and electro-reduction was conducted under aerated conditions for 20 min and 3 hrs at -0.5 V. Over 70% conversion of the nitrosamines was achieved within 20 min, and up to 90% degradation under both dilution regimes after 3 hrs (**Figure 3e**).

Discussion

Hemin catalysts are shown here to be very effective in the electroreduction of nitrosamines under a wide range of electrolyte and pH conditions, in both synthetic solutions and secondary treatment wastewater, when compared to noble-metal chemical catalysts. Surface-normalized rate constants for pseudo first-order kinetics k_{obs} estimated from the results for NDMA reduction obtained with both synthetic water and secondary effluents are given in **Table 1**. Our observed rates for NDMA degradation compare favorably

Table 1. Surface-normalized rate constants of NDMA electroreduction with hemin-CNT at -0.27 V vs SHE, calculated from conversion measurements at different electrolyte and pH conditions.

Conditions	First-order k_{obs} $\text{L}/(\text{m}^2 \text{hr})^{-1}$
100 µM NDMA, 100 mM LiClO ₄ , pH=1	~725 ^a
100 µM NDMA, 10 mM NaCl, pH=7	~650 ^a
10 ppb NDMA, secondary effluent, pH=6.9	~1800 ^b
100 ppb NDMA, secondary effluent, pH=6.9	~2600 ^b

All runs were performed at -0.5 V, in ^a5 mL and ^b10 mL volumes for 20 min. For 10 ppb and 100 ppb, estimates are based on final concentrations at 20 min.

(2-3 times higher) with those obtained with reductive electrodes such as boron-doped diamond films,¹⁷ with the latter presenting first-order rate constants of ~200-300 L/(m²hr) at current densities between 7-10 mA/cm² and higher NDMA concentrations of 500 µM and 100 mM NaClO₄. Also importantly, we conducted electroreduction at significantly lower working potentials (-0.5 V vs Ag/AgCl or -0.27 V vs SHE) than those reported previously (~ -2 to -4 V),¹⁷ while achieving current densities up to 5 mA/cm². Also, when normalized by the mass of the catalyst loading, the estimated equivalent zero-order rate constants for our hemin-CNT catalysts (50 mmol min⁻¹ g_{catalyst}) are approximately an order of magnitude higher than those observed with state-of-the art Pd-supported chemical catalysts,⁴ this result is encouraging as the earth-abundance of iron and the wide availability of hemin as a catalyst point to the better cost-effectiveness of our systems relative to others in the literature. Furthermore, hemin-CNT catalysts can sustain mass-based rate constants that are close to 2 orders of magnitude higher than many non-noble bulk metal catalysts such as iron or zinc alloys.³⁵ This high stoichiometric conversion displayed by hemins is a hallmark of metal-complex inorganic and enzyme catalysts, enabling highly-selective organic transformations due to their unique electronic structures.

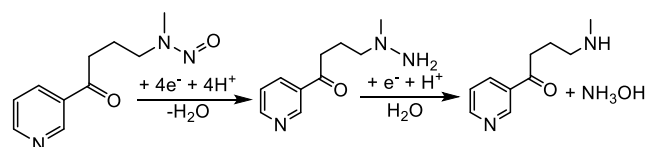


Figure 4. Electroreduction of nitrosamines (NNK as an example) in aqueous acidic solutions via formation of hydrazines and amines.

The mechanism of nitrosamine electroreduction of nicotine-derived nitrosamine ketone (NNK) and N-nitrosornicotine (NNN), which play important roles in carcinogenesis in aqueous acidic media, was elucidated using MALDI-TOF and ESI spectrometry. The detection of the transient hydrazine and amine products (see Supporting Information Section S2) during the course of electroreduction of NNK and NNN in aqueous acidic solutions affords the overall reaction schematic of their degradation shown in **Figure 4**. The binding mode is postulated to be that of the nucleophilic -N=O nitrogen with Fe(II), as observed in the interaction of a range of nitrosamines with Lewis acidic organometallic and metal complexes,^{36, 37} and of nitrosamine interactions with the P450 iron center in the context of cancer routes.³⁶⁻³⁸ Based on the potential binding mode, and the observation that acidic conditions are highly favorable for the 4-electron reduction process,¹⁸ it is proposed that the hemin-catalyzed reaction occurs through a proton-coupled electron transfer mechanism.³⁹⁻⁴¹ In the analysis of products of the electrochemical reduction of NDMA and NPYR, corresponding secondary amines were also detected, indicating that those hydrazines were further reduced electrochemically. A detailed study of this complex, multi-electron conversion is on-going.

In conclusion, we have demonstrated that hemin-functionalized redox-electrodes can be utilized as efficient heterogeneous electrocatalysts for the reduction of nitrosamines, under both synthetic conditions to study the mechanism, and at ppb-level concentrations in secondary wastewater, to evaluate its potential as a tertiary treatment. The effect of the redox-species is dramatic, as TON>700 can be achieved at very low potentials (-0.27 V vs SHE). The modular electrochemical control and high electrocatalytic performance in the reduction of nitrosamines are interesting for environmental and industrial organoelectrochemistry applications. From a fundamental perspective, this work shows the power of biomimetic design in which these iron metalloporphyrins, originally studied as a key component for nitrosamine binding in the metabolic pathway for cancer, can now be exploited in an innovative approach for water treatment and environmental remediation.

ASSOCIATED CONTENT

Supporting information – Supporting Information is available free of charge on the ACS Website.

Additional spectroscopy and characterization procedures, and images (PDF).

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