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Efficient Electrochemical Synthesis of Robust, Densely Functionalized Water Soluble Quinones

James B. Gerken,‡ Alexios Stamoulis,‡ Sung-Eun Suh,‡ Nicholas D. Fischer,‡ Yeon J. Kim,‡ Ilia A. Guzei,§ and Shannon S. Stahl*a

Conjugate addition of thiols to benzoquinones have been coupled to in situ electrochemical oxidation of the resulting hydroquinone to enable full substitution of quinone C–H bonds. The sulfonated thioether-substituted quinones exhibit high solubility and stability in aqueous solution and have redox potentials ranging from 440–750 mV vs. SHE. The electrosynthetic protocol is effective on >100 g scale.

Highly-stable, water soluble quinones are important targets for energy-related applications, such as redox flow batteries and mediated electrolys. We recently reported the design of a tetrasubstituted quinone containing four sulfonated thioether moieties (1, Scheme 1) that displays substantially enhanced stability relative to less substituted quinones of similar redox potential. Quinones with anionic groups feature improved aqueous solubility and membrane impermeability. The thioether-tethered sulfonates were identified as a particularly conveniently installed anionic group, and substitution at all positions on the quinone ring significantly enhances the stability of the quinone. The thioether linkage is robust with respect to substitution in aqueous acid at elevated temperatures over prolonged periods. Herein, we describe an electrosynthetic protocol that provides efficient and scalable access to 1 and a series of other substituted quinones.

In previous work, we pursued the synthesis of 1 using two established methods. The first employed addition/elimination reactions with chloranil, involving nucleophilic substitution of the chloride substituents by thiols (Scheme 1a). The low yield of desired product obtained from this protocol, however, prompted us to evaluate a conjugate addition/oxidation sequence (Scheme 1b). Thiols are particularly effective nucleophiles for conjugate addition to benzoquinone (BQ), and the hydroquinone obtained from nucleophilic addition can be oxidized by unreacted BQ. This process may be repeated until the quinone is fully substituted, ultimately enabling the synthesis of tetrathioether hydroquinones. The resulting reaction mixture, however, contains significant quantities of hydroquinone (at least 4 equiv) and/or partially substituted quinone byproducts, complicating product isolation and limiting the yield of the desired product. These issues motivated efforts to identify an alternative synthetic protocol that could be used to prepare substituted quinones. The data outlined below show that electrochemical oxidation methods allow for effective...
synthesis of thioether-substituted quinones starting from either quinones or hydroquinones. Benzoquinones are susceptible to conjugate addition at ring carbons bearing C–H bonds to form functionalized hydroquinones. The resulting hydroquinones can undergo electrochemical oxidation to the corresponding benzoquinones at potentials determined by their substituents. Electrochemical oxidation of hydroquinones and catechols in the presence of nucleophiles has been demonstrated previously to form substituted quinone products, but this process commonly leads to addition of a single nucleophile due to the higher reduction potential of the quinone following nucleophile addition. Addition of a thiol, however, lowers the potential of the resulting thioether quinone by approximately 20 mV. This insight provides the basis for an electrochemical approach to achieve complete thioetherification of the C–H positions in BQ and other substituted BQ derivatives by conducting the electrolysis of the quinone in the presence of a sulfonated alkyl thiol (Scheme 2a). Use of this class of nucleophiles is especially felicitous since the sulfonate group and its counterion may serve as the supporting electrolyte for the electrochemical reaction.

Initial voltammetry experiments showed that the sodium mercaptoethylsulfonate (MESNa) nucleophile exhibited no redox behavior at a glassy carbon electrode at the potential of the H2Q/BQ redox couple at pH 1. Therefore, bulk electrolysis experiments were conducted with reticulated vitreous carbon (RVC) as the anode material (Table 1). Acidic conditions were employed (pH 1) to favor H2 evolution as the cathodic reaction. Constant potential electrolysis was performed at a potential chosen to ensure complete oxidation of the hydroquinone that formed during the oxidative coupling reaction. An initial experiment was conducted by stirring 4 equiv of MESNa and BQ, with an RVC anode and Pt wire counter electrode. Considerable charge was passed but negligible conversion was apparent. This failure was traced to the use of stirring, as the same experiment conducted with a lack of stirring led to nearly quantitative product formation (Entries 1 vs. 2). Because minor variations in the electrode potential did not have a deleterious effect on the product yield (Entries 2 and 3), the electrolysis was then conducted under constant current using currents similar to those observed in the constant potential experiments (Entries 4 and 5). Larger scale reactions (≥ 10 g) made it impractical to use Pt wire; however, Ni wire proved to be an effective counter electrode. Finally, the reaction sodium mercaptopropylsulfonate (MPSNa) was conducted on 100 g scale, using H2Q as the substrate to avoid exposure to BQ (Entry 6). As the reaction was scaled up, the substrate concentration was kept constant while the sizes of the electrodes were proportionately increased, and the current was increased to keep the reaction time roughly constant. Excellent yields of tetrathioether quinones 1 and 2 were obtained under the optimized, constant current conditions (Scheme 2b; see ESI† for details).

Several considerations account for the success of these reactions. In an undivided cell, the pH remains constant, because the anode reaction produces the same quantity of H+ ions as are consumed at the cathode. Very slow convection (i.e., no stirring) is necessary because quinones formed at the anode are transported to the cathode and reduced quickly relative to the rate at which they react with thiols, leading to lower current efficiency. It was possible to scale the reactions in ordinary
laboratory glassware using a simple power supply to prepare ≥10–100 g of the desired quinones (Scheme 2c,d).

The slow mass transport, which is necessary to avoid unproductive redox cycling, leads to significant concentration gradients during the electrolysis, evident by the colour of the quinone intermediates. The anodic oxidation reaction could involve the starting hydroquinone, an intermediate thioether hydroquinone, or the tetrasubstituted hydroquinone product. Additional redox reactions may take place away from the electrode to produce a substituted quinone that can react with a thiol. This combination of anodic and solution-phase processes afford quinone derivatives that are eventually converted into the fully substituted product.

Varying the thiol and quinone or hydroquinone starting materials enabled the synthesis of a series of different thioether quinone products. The yields of these compounds are summarized in Scheme 3, together with their redox potentials and their aqueous solubilities. Low-potential quinones, such as the precursors to 3 and 10, react more slowly with thiols. To avoid side reactions, these products were synthesized via electrolysis with constant potential rather than constant current (see ESI† for details). The synthesis of 3 was begun from the quinone. Side reactions with solvent during the reactive dissolution of 3 (cf. step 1 in Scheme 2b) prior to electrolysis led to insoluble material and presumably account for the lower yield of 3.

Higher potential quinones, such as the precursors to 8 and 9, are effective H-atom abstracting agents and open a pathway to formation of disulphide by-products, competing with the desired nucleophilic addition reactions with thiols. Thus, modified conditions were required to generate acceptable yields of conjugate addition products instead of quinone-catalyzed disulfide formation. In the case of 8, it was possible to access the product by slowly adding the thiol during the course of the reaction. Although excess thiol was required due to formation of disulfide by-product (6 equiv of RSH, rather than the theoretical amount of 2 equiv), the desired product was obtained in 86% yield. In the case of 9, selectivity was achieved by increasing the pH. At higher pH, enough thiolate is formed that nucleophilic addition and C–S bond formation is favoured over competing S–S bond formation. In this manner, quinone 9 was obtained from catechol in pH 7.5, 0.1 M phosphate buffer.18 In general, it is noteworthy that the reactions afford the observed thioether products despite the fact that the benzoquinone reduction potentials can be >500 mV higher than typical disulfide reduction potentials (for reduction potentials of the starting materials, see Table S1).11,19

Presumably, this selectivity arises from the much more facile electrochemical kinetics for hydroquinone oxidation than thiol dimerization at a carbon electrode.

Isolation of the reaction products as a salt of a (poly)sulfonate is straightforward in most cases. The electrolysis is performed at concentrations near the solubility limit of the product (Scheme 3 and Table S1), and the product typically precipitates in high purity on dilution of the reaction mixture with a water-miscible, but less polar solvent, such as ethanol or acetone. The traces of incompletely substituted products or starting material, being less charged, are more soluble in the mixed solvent and are removed by filtration.

Some additional observations emerging from the preparation of these derivatives are worth noting. If the hydroquinone is poorly soluble in water, it can be advantageous to use a mixed solvent system. This approach was used in the synthesis of 3, 6, and 10, which employed acetone as a co-solvent. Complete solubility of the hydroquinone is not necessary; only enough is required to allow the desired current to pass. Further dissolution is facilitated by formation of more soluble products that can undergo reoxidation to soluble quinones. These quinones can then mediate redox reactions with the starting hydroquinone to a quinone that undergoes reactive dissolution with the thiol. In recalcitrant cases (e.g., 2-phenylhydroquinone), it is advantageous to start with the quinone so that the process begins with the reactive dissolution to form a more-soluble product that can undergo electrochemical formation of the remaining thiethers. This tactic is opposite to the one employed by Nematollahi and Tammarri, in which the lower solubility of the reaction product was used to achieve selective mono-thioetherification.13

![Scheme 3. Isolated yields, reduction potentials, and aqueous solubilities of electrosynthesized hydroquinone products. *100 g scale, †10 g scale, ‡constant potential electrolysis. General reaction conditions: H2O (10 mmol), RSH 1.1 equiv (n = # of equivalents needed for full substitution), 0.2 M in H2O/EtOH (See ESI† for details).](image)

![Figure 1. A molecular drawing of 2 asymmetric units of the crystal structure showing the structure of the quinone form of 2 drawn with 50% probability ellipsoids.](image)
On extended electrolysis, the fully substituted product is at least partially oxidized to the corresponding quinone. Redox cycling of this quinone back to the hydroquinone at the cathode prevents the electrode potential from rising to a point where decomposition reactions become fast. The quinone form of compound 2, obtained by running the electrolysis reaction for longer than usual, led to the formation of crystals that were suitable for X-ray crystallographic analysis. The X-ray data are in accord with the proposed product (Figure 1). Similar crystallographic decomposition reactions become fast. The quinone form of compound 2 generally prevents the electrode potential from rising to a point where the nucleophile reoxidation at potentials tolerated by the nucleophile. The success of these variations is partially supported by NSF CHE-0342998, NSF CHE-1048642, a UW Madison Instructional Laboratory Modernization Award, a gift from Paul J. and Margaret M. Bender, and by NIH S10 OD012245. Mass spectrometry equipment was partially supported by NIH 1S10 OD020022-1.

**Notes and references**

8. Thiosilanes have been used effectively as well: N. A. Romero, W. O. Parker Jr., and T. M. Swager, *Macromolecules* 2019, DOI: 10.1021/acs.macromol.9b01855.
16. Occasionally, disubstitution is observed, such as in the formation of 2,3-dicyanohydroquinone from benzoquinone and cyanide via the intercession of an enedione intermediate. See, for example: G. J. Perry and M. D. Sutherland, *Tetrahedron* 1982, 38, 1471-1476.
18. Despite the success of these variations, some limitations to the method have also been observed. For example, the high nucleophilicity of the thiol resulted in displacement of sulphonate, cyano, and trifluoracetetyl groups from quinone precursors, ultimately, affording low yields of the product.