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A R T I C L E S

A Substituent Effects Study Reveals the Kinetic Pathway for an Interfacial Reaction

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Abstract: This paper describes the use of a substituent effects study to understand the mechanistic basis for an interfacial Diels−Alder reaction that does not proceed with standard second-order kinetics. Cyclopentadiene (Cp) undergoes a Diels−Alder reaction with a chemisorbed mercaptobenzoquinone to yield an immobilized Diels−Alder adduct. The pseudo-first-order rate constants are not linearly related to the concentration of diene, but they reach a limiting value with increasing concentrations of diene. The results of a substituent effects study support a mechanism wherein the electrochemical oxidation of hydroquinone produces two states of quinone. The first form, Q*, either reacts with Cp or isomerizes to Q, a form that is significantly less reactive with the diene. The interfacial reaction reaches a maximum rate when the concentration of diene is sufficiently high so that Q* undergoes complete Diels−Alder reaction and does not isomerize to Q. This work provides an example of the use of physical organic chemistry to understand an interfacial reaction.

Introduction

Reactions that occur at a solid−liquid interface can differ substantially from the corresponding solution-phase reactions.[1,2] These differences, as well as the mechanistic factors that influence interfacial reactions, remain poorly understood. The rates and products of interfacial reactions, for example, often show unexpected and substantial dependences on surface structure. The number of examples[2] that clearly address these issues is limited, in large part, because of the difficulty in devising model systems that have well-defined environments about the reactions and that permit good kinetic measurements of the reactions. This challenge has made it difficult to apply standard approaches of physical organic chemistry to interfacial reactions. In this paper, we report a significant advance in this direction and describe the use of a substituent effects study to understand the mechanistic basis for an interfacial Diels−Alder reaction that does not proceed with standard second-order kinetics.

Results and Discussion

The Diels−Alder reaction addressed in this study is illustrated in Figure 1. Mercaptobenzoquinone groups that are chemisorbed to a gold substrate react with cyclopentadiene in a contacting solution to give the Diels−Alder adduct.[3] The benzoquinone groups undergo a reversible electrochemical reduction to yield the corresponding hydroquinone and, therefore, permit the use of cyclic voltammetry to measure the rate of the reaction. A series of cyclic voltammograms acquired during the reaction show that the waves for reduction of the quinone decrease with time as the benzoquinone groups are converted to the redox-inactive Diels−Alder adduct (Figure 1).[3−5] The formation of product was confirmed by reflectance infrared spectroscopy and ellipsometry.[3] Surprisingly, we found that this reaction does not proceed by a second-order process. Although the reaction displays well-behaved pseudo-first-order rate constants, these first-order rate constants are not linearly related to the concentration of diene, but instead, they reach a limiting value with increasing concentration of diene.

We considered two mechanistic models that are consistent with the observation of a rate maximum with increasing concentrations of diene. (i) The diene associates with the monolayer in a pre-equilibrium step, with an association constant of K_{ads},

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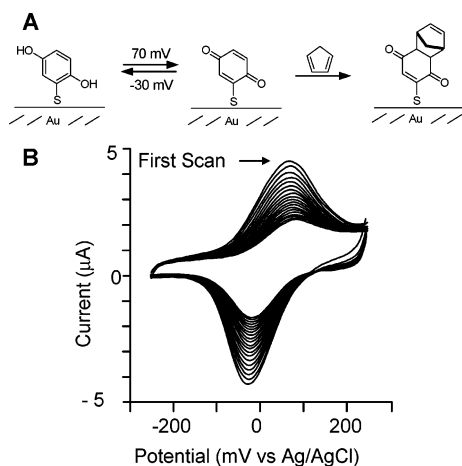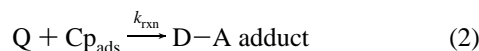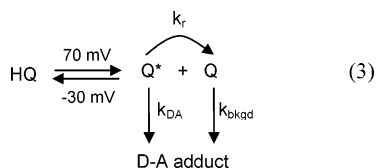(5) Kwon, Y.; Mrksich, M. *J. Am. Chem. Soc.* **2002**, *124*, 806−812.

Figure 1. (A) This work reports on the Diels−Alder reaction between cyclopentadiene and mercaptobenzoquinone immobilized to a gold surface. The rate of the reaction is monitored using cyclic voltammetry to observe the reversible redox couple between benzoquinone and hydroquinone. (B) A series of cyclic voltammograms show that the peaks for oxidation of hydroquinone diminish with time as the quinone reacts with cyclopentadiene to form the Diels−Alder adduct.

to generate a "unimolecular" intermediate (Cp_{ads}; eq 1) that then reacts to give the cycloadduct (D−A adduct), with a second-order rate constant of k_{rxn} (eq 2).[3]

$$Cp \underset{}{\overset{K_{ads}}{\rightleftharpoons}} Cp_{ads} \qquad (1)$$

$$Q + Cp_{ads} \xrightarrow{k_{rxn}} D-A \text{ adduct} \qquad (2)$$

(ii) Electrochemical oxidation of the hydroquinone (HQ) generates a "reactive" quinone (Q*) that either reacts with the diene, with a second-order rate constant of k_{DA}, or isomerizes to an "unreactive" quinone (Q), with a rate constant of k_r. Q then reacts with diene, with a second-order rate constant of k_{bkgd} (eq 3).

$$HQ \underset{-30 \text{ mV}}{\overset{70 \text{ mV}}{\rightleftharpoons}} Q^* + Q \qquad (3)$$

$$\downarrow k_{DA} \quad \downarrow k_{bkgd}$$

$$D\text{-}A \text{ adduct}$$

In both models, the rate reaches a maximum at high concentrations of diene. In the first model (the pre-association model), the maximum rate is observed at concentrations of diene that give complete adsorption of diene to all sites in the monolayer. The magnitude of the maximum rate reflects the reactivity of the diene and quinone and should therefore change with substitution of the diene. In the second model (the activated dienophile model), the maximum rate reflects the generation of Q* and is independent of diene structure. Hence, the two mechanisms can be experimentally distinguished by determining whether the rate constant for the Diels−Alder reaction increases with the reactivity of the diene partner. On the basis of this reasoning, we employed a substituent effects study using a series of substituted cyclopentadienes.[6,7]

We first measured rate constants for the Diels−Alder reaction of a series of dienes with a monolayer presenting benzoquinone groups at 10% density among hydroxyl-terminated

alkanethiolates. We have previously shown that the Diels−Alder reaction on this monolayer proceeds with a second-order rate constant and therefore in a mechanistically analogous manner to the solution reaction.[4,5] These studies serve to establish the relative rate constants for the series of substituted cyclopentadienes.

A series of dienes that ranged in steric and electronic character (cyclopentadiene (Cp), methylcyclopentadiene (MeCp), 1,2,3,4,5-pentamethylcyclopentadiene (Me_5Cp), *tert*-butylcyclopentadiene, 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene, and 1,2,3,4,5,5-hexachlorocyclopentadiene) were chosen for this study. Three of the dienes (Cp, MeCp, and Me_5Cp) reacted efficiently with the immobilized mercaptobenzoquinone and are described below. We found that the dienes with electron-withdrawing groups or with the sterically demanding *tert*-butyl group did not undergo significant reaction with the quinone over the time course of a typical experiment and were therefore not used further in these studies.

The three remaining dienes (Cp, MeCp, and Me_5Cp) displayed a similar kinetic behavior. In each case, the reaction of the diene with the immobilized quinone proceeded with a well-behaved pseudo-first-order rate constant. When the reaction experiments were performed for a series of concentrations of each diene, we found that the first-order rate constants initially increased linearly with diene concentration but then reached a limiting value at higher concentrations of diene (Figure 2A−C).

A comparison of the three rate profiles leads to two important observations. First, the maximum rates (v_{max}, Table 1) for the three dienes varied by less than a factor of 2. The similarity of these rates suggests that the reaction velocity is independent of diene structure and argues against a mechanistic model that invokes adsorption of the diene to the surface prior to reaction. We also note that the limit in rate is not due to a steric crowding at the solid interface because the larger Me_5Cp does not react slower than Cp.

To be certain that the intrinsic reactivity of the dienes spans a larger range than observed above, and to rule out mass-transport effects as a rate-determining influence, we determined rate constants for the three dienes using the control monolayer system. Monolayers were prepared from a benzoquinone-terminated undecanethiol and 1-mercaptoundecan-11-ol groups in a ratio of 1:9. These monolayers were reacted with each of the three dienes under conditions identical to those described for the substrates having chemisorbed mercaptobenzoquinone. All three dienes reacted efficiently with the tethered quinone, and the reactions proceeded with second-order kinetics (Figure 2D−F). Importantly, the three dienes reacted with second-order rate constants (k_{DA}) that reflected the influence of the electron-donating methyl groups[6−12] (Table 1, Figure 2D−F). The addition of one methyl substituent to Cp resulted in a 13-fold greater rate, and the addition of five methyl substituents re-

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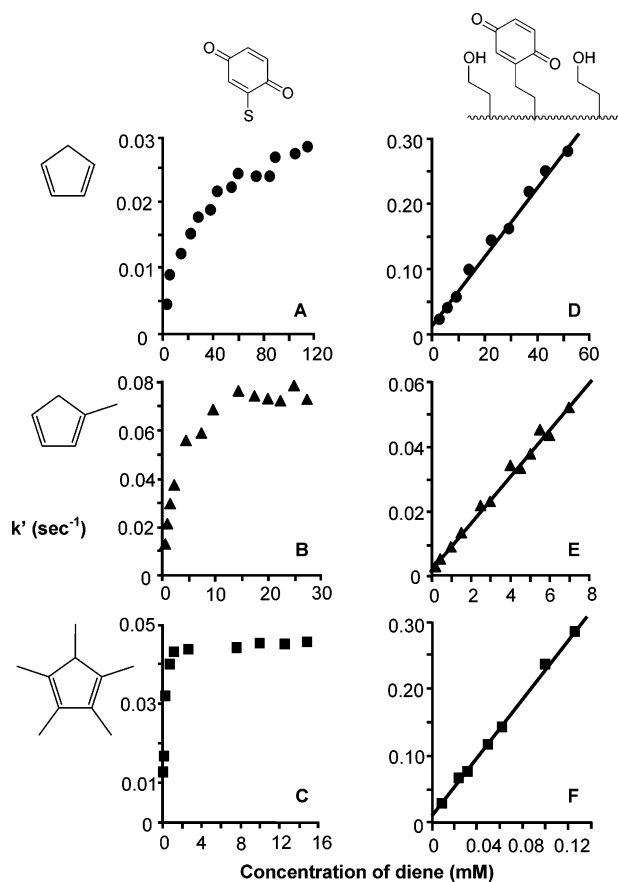(12) Letourneau, J. E.; Wellman, M. A.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 7272−7277.

Figure 2. Determination of rate constants by plotting pseudo-first-order rate constants over a range of diene concentrations. (Left column; 2A−C) The rate of the reaction reaches a limiting value and is not consistent with a second-order reaction. (Right column; 2D−F) In a control system, the Diels−Alder reactions between the dienes and a quinone immobilized to a self-assembled monolayer do proceed with second-order kinetics. Plots of first-order rate constants, k', over a series of diene concentrations are linear and provide the rate constants, k_{DA}. Note that the numerical ranges on the axes differ for the plots.

Table 1. Kinetic Data for Substituent Effects for the Diels−Alder Reaction

| diene | alkanethiol | mercaptohydroquinone[a] | |
	k_{DA} (M^{-1} s^{-1})[b]	k_{DA} (M^{-1} s^{-1})[c]	ν_{max} (s^{-1})[d]
Cp	0.54	0.50	0.033
MeCp	7.10	12	0.084
Me$_5$Cp	220	180	0.045

[a] Data in the second and third columns report the kinetic constants for reaction of dienes with the chemisorbed quinone and were determined from the plots in Figure 2A−C. [b] Second-order rate constants, obtained with alkanethiol self-assembled monolayers that present the quinone group. The rate constants were determined from the slope of the linear plots in Figure 2D−F. [c] Second-order rate constants are the linear fits to the initial portion of the plots in Figure 2A−C. [d] Maximum observed first-order rates.

candidate inhibitors had no effect on the value of $E_{1/2}$ observed for the redox couple of the quinone, which would be expected if they were associating with the surface and altering the environment of the redox-active quinone. These experiments therefore provide further evidence against adsorption of diene as a part of the rate-determining step in the reaction.

The second important observation from Figure 2A−C is that at low concentrations of diene, where the first-order rate constants increase linearly with diene concentration, the reaction rates were very clearly dependent on the structure and reactivity of the dienes. This linear relationship suggests that the reaction proceeds with a second-order rate constant for low concentrations of diene. We determined the second-order rate constant, k_{DA} (eq 3), from the slope of the best-fit line to the initial linear portion of the curve. The rate constants, k_{DA}, increased with the addition of electron-donating groups, Me$_5$Cp > MeCp > Cp. Further, the rate constants were strikingly similar to those found in reactions of the dienes with a quinone tethered to a monolayer (Table 1). Therefore, we conclude that the interfacial Diels−Alder reaction reacts in a second-order process for low concentrations of diene and then tends toward a limiting velocity with increasing concentrations of diene.

The observation that the reaction rates for low concentrations of dienes reflect the intrinsic reactivity of the dienes is consistent with the activated dienophile model, in which the electrochemical cycling generates a reactive form of the quinone, Q*, that either reacts with diene or isomerizes to a nonreactive form, Q (eq 3). To directly test the hypothesis that the reaction requires this electrochemical generation of Q*, we determined the rate of the reaction at a range of scan rates in the cyclic voltammetry.

First-order rate constants were determined at three concentrations of Me$_5$Cp (0.0153, 0.125, and 5 mM) and four scan rates (25, 50, 75, and 100 mV/s). The three concentrations were chosen to represent the three regimes in the rate behavior of the reaction (as shown in Figure 2C): the linear increase in pseudo-first-order rate constants, the deviation in rate constant from linear behavior, and the maximum rate constant. At each concentration, the first-order rate constants increased linearly with the scan rate (Figure 3). This observation unambiguously implicates the redox cycle in the reaction and definitively rules out the pre-association model.

While this analysis establishes the generation of a reactive quinone (Q*) and accounts for the relative rates of dienes at high and low concentrations, it does not address the modest differences in maximum rate for the three dienes. The maximum rates for the three dienes differ by a factor of 2, which

sulted in a 400-fold increase in reaction rate relative to the unsubstituted Cp.

A comparison of the reaction of the three dienes with quinone groups tethered to a self-assembled monolayer and directly chemisorbed to a gold film establishes that the maximum rate of reaction in the latter system is not influenced by the intrinsic reactivity of the diene or limited by mass-transport effects. Hence, these data rule out the mechanistic model that is based on a pre-association of the diene with the substrate.

We also performed a series of inhibition experiments that further serve to rule out the pre-association model. This model invokes an intermediate, having the diene adsorbed to the substrate, and leads to the hypothesis that small molecules that share the shape and properties of Cp (but not its reactivity toward quinone) could bind to the surface and competitively inhibit the association of Cp and, therefore, decrease the rate of reaction.[13] We found that several candidate inhibitors, including furan, cyclopentene, 1,4-cyclohexadiene, and benzene, had no effect on the reaction rate, even at concentrations near their solubility limit. Further, we found that the presence of these

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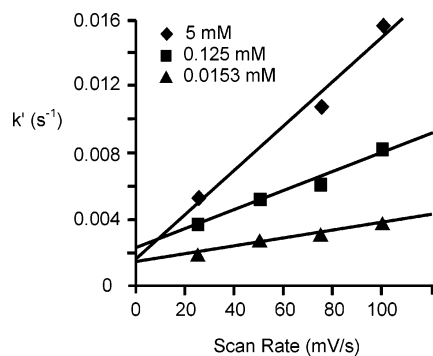
Figure 3. Observed rate of the reaction of Me$_5$Cp is linearly dependent on the rate at which the potential is scanned in the cyclic voltammetry. The observed first-order rate constants, calculated from the decay in CV intensity, were plotted against the rate at which the potential was scanned.
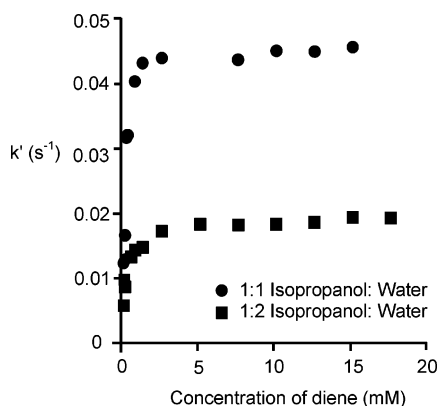

Figure 4. Observed maximum rate of the reaction is dependent on the composition of solvent. The rate in 1:1 2-propanol/phosphate-buffered saline is 2-fold faster than that in 1:2.

corresponds to a difference of 0.5 kcal/mol in transition-state energy ($\Delta\Delta G^{\ddagger}$). We believe that the differences in the transition-state energy are most likely due to differences in solvation at the interface that arise as the interfacial Diels−Alder reaction proceeds. Each of the Diels−Alder adducts will have differences in interfacial solvent and ion structure, which could reasonably account for the small differences in transition-state energies. Indeed, we observed a 2-fold decrease in the maximum rate when the composition of solvent was changed from 1:1 2-propanol/water to 1:2 2-propanol/water (Figure 4). This result indicates that differences in solvation of the diene can account for the small differences seen in the maximum rates for the three dienes.

What is left in this analysis is to measure the individual reaction rates of Q and Q* with diene and to understand the structures of Q and Q*. We first note that the electrochemical oxidation of HQ must generate a mixture of Q and Q*; if the oxidation generated only Q*, then the reaction would be complete in a single voltammetric scan. By measuring the extent of reaction after each scan, using concentrations of diene that give maximum rate, we estimate that approximately 25−30% of the hydroquinone is converted to Q*, with the remaining fraction converted directly to Q. Because both Q and Q* can participate in the D−A reaction with the diene, it is important to determine the rate of reaction of both forms of the diene. To asses the rate of reaction of Q with Me$_5$Cp, we determined the rate constant, k_{bkgd}, in the absence of electrochemical cycling. The experiment was performed as follows. The hydroquinone

was electrochemically oxidized to quinone; Me$_5$Cp was added after a period of time sufficient for all of the Q* to isomerize to the Q; the reaction was allowed to proceed for a specified period of time; the quinone was then reduced to give the hydroquinone. We completed this experiment for a series of time points (1, 3, 7, and 14 min) to determine pseudo-first-order rate constants for a range of diene concentrations (0.0153, 0.06125, 0.153, and 5 mM). These pseudo-first-order rate constants were then used to calculate a second-order rate constant for the interfacial reaction between Q and Me$_5$Cp. The reaction between Q and Me$_5$Cp proceeded with a second-order rate constant (k_{bkgd}) of approximately 2 M^{-1} s^{-1}. This rate constant is approximately 2 orders of magnitude slower than that measured for Q* ($k_{DA} = 220$ M^{-1} s^{-1}). This finding adds further support for a model that invokes two forms of the quinone.

These experiments do not address the physical nature of Q and Q*. We first reasoned that Q* was a radical species that is an intermediate in the two-electron oxidation of hydroquinone.[10,12] To test this possibility, we performed the reaction experiment in the presence of radical traps (at concentrations of 5 mM) that should intercept the reactive intermediate. Both the carbon radical trap (2,2,6,6-tetramethyl-1-peperinyloxy)[14] and the oxygen, carbon, or sulfur radical trap (2,2,4-trimethyl-2*H*-imidazole-1-oxide)[15] showed no effect on the reaction rate. Therefore, we believe that Q* is not a radical species.

One reasonable possibility is that Q* and Q have different physical orientations on the gold substrate, with corresponding differences in reactivity, but the structural details of those states are difficult to ascertain.[16] For example, Q could be oriented perpendicular to the surface,[13] while Q* is slanted on the surface, leading to a more-accessible position of the diene's π system that participates in the Diels−Alder reaction.

A second possibility is that the electrochemical cycling is producing a more-reactive quinone species by providing for a direct interaction between the carbonyl group of the quinone and the gold substrate. It has been shown in infrared studies that molecules under electrochemical control, such as uracil, can chemically interact with the gold electrode surface through exocyclic oxygen interactions with the surface.[17] A transient interaction between the carbonyl oxygen of the benzoquinone and the gold surface would remove electron density from the benzoquinone and lower the energy of the LUMO. In this case, the gold would be effectively acting as an electron-withdrawing group on the dienophile and would enhance the rate of the reaction. This proposal is consistent with the activated dienophile model wherein a reactive quinone, Q*, is produced by electrochemical oxidation, which can either react with the diene or isomerize to a less reactive state, Q, because there is no longer an electron-withdrawing group on the dienophile to enhance the rate of the reaction.

Conclusions

This work has investigated an interfacial Diels−Alder reaction that proceeds with an unexpected kinetic profile. We employed

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a substituent effects study to differentiate between a model that invokes adsorption of the soluble diene and a model that invokes an electrochemically induced activation of the quinone for reaction with diene. The results of these kinetic studies are consistent with the second model, wherein the electrochemical oxidation of hydroquinone generates two forms of quinone, Q* and Q, in a fixed ratio during each cycle. Q* is a "reactive" species that rapidly reacts with diene or isomerizes to Q. Q is an "unreactive" species that reacts with diene 100-fold slower than does Q*. At low diene concentrations, the rate for reaction of diene with Q* is slow relative to the rate for isomerization of Q* to Q; in this limit, the observed rate is first order in diene and shows the expected dependence on diene structure. At higher concentrations of diene, the Diels−Alder rate is fast relative to the rate of isomerization of Q*; in this limit, the rate-limiting step is the generation of Q* and is therefore independent of the diene structure.

This study is also significant because it gives an example of applying traditional solution-phase physical organic probes, including substituent effects and radical traps, to investigate the mechanistic course of an interfacial reaction. This combination enables mechanistic studies of interfacial reactions that have largely been limited to solution reactions. We believe that the strategy described here will grow in importance as organic chemists further exploit interfacial reactions and seek to control these systems.

Experimental Section

Chemicals were purchased from Aldrich and Fisher Chemical Companies. For electrochemistry, phosphate-buffered saline was purchased from Gibco. Cyclopentadiene and methylcyclopentadiene were distilled prior to each use to remove the dimer and stored at −20 °C as a 5 mM solution in 2-propanol. Mercaptobenzoquinone and 11-(2,5-dihydroxyl)-1-mercaptoundecane were synthesized as previously described.[3,5]

Preparation of Monolayer Substrates. Gold substrates were prepared by vacuum deposition of titanium (125 Å) followed by gold (1000 Å) onto silicon wafers (1111, Silicon Sense) using a Thermionics evaporator. Mercaptobenzoquinone monolayers were formed by immersing the gold-coated substrates in a 10 mM ethanolic solution for 1 h. Mixed monolayers were formed by immersing the gold substrates in an ethanolic solution (1 mM total (9:1)) of 1-mercaptoundecan-11-ol and 11-(2,5-dihydroxylbenzene)-1-mercaptoundecane for 12 h. The substrates were removed from the solution, washed with absolute ethanol and deionized water, and dried with a stream of nitrogen gas.

Electrochemical Measurements. Cyclic voltammetry was performed using a Bioanalytical Systems CV-50W potentiostat in an electrolyte solution comprising equal parts of 2-propanol and phosphate-buffered saline solution. The pH of the electrolyte solution was adjusted to 7.4 with 0.1 N HCl and 1 N NaOH solutions. All of the experiments used the monolayer as a working electrode, a platinum wire counter-electrode, and a Ag/AgCl reference electrode. Cyclic scans were performed between −250 and +250 mV on the mercaptobenzoquinone monolayers and between −400 and +600 mV at a scan rate of 100 mV/s, unless otherwise indicated. Soluble diene was added to the electrolyte solution in varying concentrations.

Inhibition Experiments. Cyclic voltammetry was performed as described above with a varying concentration (0.5−100 mM) of inhibitor added to the solution.

Scan Rate Dependence. Cyclic voltammetry was performed as described above at scan rates of 25, 50, 75, and 100 mV/s over a range of Me_5Cp concentrations (0.0153, 0.125, and 5 mM).

Solvent Dependence. Cyclic voltammetry was performed as described above in an electrolyte solution of one part 2-propanol to two parts phosphate-buffered saline. The pH was adjusted to 7.4.

Background Rate Determination. The electrochemical cell and electrolyte were used as described above. The working electrode (monolayer) was reduced to determine the intensity of the reduction peak and, thus, the density of quinone on the surface, and was then oxidized to transform the monolayer into reactive quinone groups. Diene was then added, and the reactants were allowed to react for 1, 3, 7, or 14 min. Then, the electrode was reduced, and the intensity of the reduction peak was measured. This series of scans was done for four concentrations of Me_5Cp (0.0153, 0.06125, 0.125, and 5 mM).

Radical Trap. The electrochemical cell and electrolyte were used as described above. Soluble radical traps (2,2,6,6-tetramethyl-1-peperinyloxy or 2,2,4-trimethyl-2*H*-imidazole-1-oxide) were added to the electrolyte solution in varying concentrations between 1.2 and 6 mM. Diene was not added to the solution.