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Radical Anion Reactions of Cyclobutane Derivatives: Electron-Transfer Cleavage of Dithymoquinone

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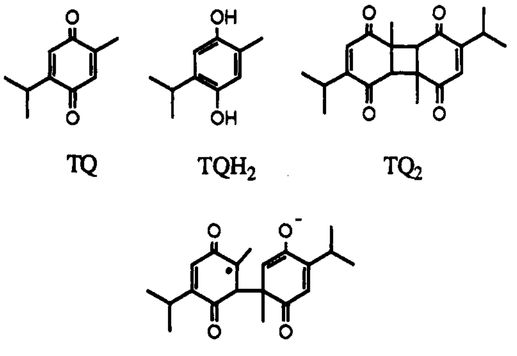
Summary: One-electron reduction of dithymoquinone, a quinone cyclobutane dimer, results in its cleavage to the monomeric quinone with a rate constant of 3.0 s^{-1}.

Chemical reactions that are initiated by single-electron transfer are of both fundamental and practical importance.[1] Radical cation pericyclic reactions have received considerable attention because of their ability to form and cleave C–C bonds.[2] In contrast, very little is known about the corresponding radical anion pericyclic reactions. This work concerns net [2 + 2] cycloreversions that occur through radical anions. The only example of this process which has been extensively examined is the catalytic mechanism of DNA photolyase enzymes.[3] These remarkable enzymes utilize a photon of visible light to mediate cleavage of pyrimidine dimers. The cleavage step may be initiated by electron transfer from the enzyme to the substrate.[4] Radical anions of the pyrimidine dimers cleave very rapidly[5]—with rate constants in excess of 10^6 s^{-1}. One unresolved issue is why the anion radical cleavage of pyrimidine dimers is so facile. Therefore, it was of interest to determine if any other types of cyclobutane derivatives cleave upon single electron reduction, and if their cleavage would be equally facile. We report here that the cyclobutyl dimer of a quinone, dithymoquinone[6] (TQ_2, see Chart I) also cleaves upon single electron reduction but much more slowly than the pyrimidine dimers.

Chart I



TQ TQH₂ TQ₂

1

Controlled potential (−1670 mV vs ferrocene) electrolysis of TQ_2 was carried out in a 0.1 M solution of Bu_4NPF_6 in CH_3CN, held at 0 °C, using a Pt working electrode and a glassy carbon counterelectrode. The major product is TQH_2 (65%) as determined by HPLC analysis of the reaction mixture. The retention times and response factors for TQH_2 were determined by comparison to authentic samples.[7] It is important to realize that the electrolysis potential is sufficiently negative to promote the reduction of the neutral monomer, TQ. The latter exhibits two reversible reduction waves at −895 mV and −1650 mV in anhydrous CH_3CN.

Cyclic voltammetry (CV) experiments were carried out on TQ_2 in order to determine the number of electrons involved in the cleavage reaction and to estimate its rate. As shown in Figure 1, at rapid scan rates a cathodic (A) and an anodic (B) wave with $E^{\circ\prime}$ of −1360 mV is observed.[8] These peaks correspond, respectively, to the one-electron reduction of TQ_2 and the reverse process. As the scan rate is reduced, the anodic peak B diminishes and two other peaks, C and D, appear at more positive potentials. Significantly, peak D does not appear on the initial scan, instead it occurs only on scans subsequent to the initial reduction of TQ_2 (i.e., second cathodic scan). When the electrode is initially held at −1670 mV and then scanned, peaks C and D are increased relative to A and B.

We interpret these data in terms of the $E_rC_iE_r$ mechanism shown in eq 1. Initial reduction of TQ_2 forms its

$$TQ_2 + e^- \underset{B}{\overset{A}{\rightleftharpoons}} TQ_2^{\bullet -} \xrightarrow{k_{cl}} TQ + TQ^{\bullet -} \underset{D}{\overset{C}{\rightleftharpoons}} 2TQ + e^- \quad (1)$$

anion radical. The latter can either reoxidize or undergo fragmentation to form TQ and $TQ^{\bullet -}$. The peaks C and D are assigned to the monomer, $TQ/TQ^{\bullet -}$. This mechanism is supported by two additional observations. First, the C and D waves appear at precisely the same potential observed for an authentic sample of TQ ($E^{\circ\prime}$ = −895 mV). Second, if TQ is added to the mixture, peak D is present

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(6) Synthesis of the substrate, TQ_2, was carried out by irradiation of a thin film of TQ on borosilicate glass using a 400-W Hg vapor lamp (yield 29%; mp 200–201 °C (lit. mp 199–200 °C)). (a) Zavarin, E. *J. Org. Chem.* **1958**, *23*, 47. This forms the anti, head-tail dimer: (b) Robbins, R. J.; Falvey, D. E. *Tetrahedron Lett.*, in press. The dimer was shown to be free (<1%) of TQ by HPLC.

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(8) Because of the unreliability of the Ag wire reference electrode, the potentials were determined by comparison to ferrocene, which was added as an internal standard. $E_{1/2}$ for ferrocene was considered to be +0.175 vs SCE: Denisovich, L. I.; Zajurin, N. V.; Bezrukova, A. A.; Gubin, S. P. *J. Organomet. Chem.* **1974**, *81*, 207.

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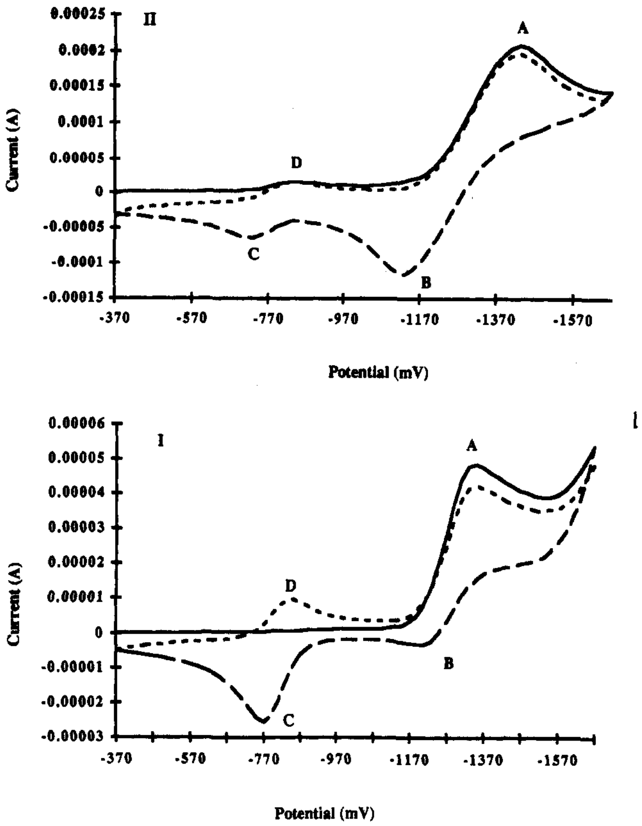

Figure 1. CV waveforms for the reduction of TQ_2 in CH_3CN/(0.1 M Bu_4NPF_6). The scan rates are (I) 100 mV/s and (II) 5000 mV/s. Peaks C and D appears only after the initial scan. Because of the unreliability of the Ag electrode, the potentials shown in the diagram are based on the $E_{1/2}$ for ferrocene (+175 mV) which was added as an internal standard (not shown). The waveforms were collected using a BAS 100A electrochemical analyzer.

on the initial cathodic scan, the C/D waves are increased, and no additional peaks are observed.

The one-electron cleavage mechanism is further verified by measurement of the scan rate dependence of the peak currents. Normally, the peak current, I_p, of a CV wave depends on the square root of the scan rate, $\nu^{1/2}$, as well as the number of electrons involved in the reaction, n, as described in eq 2.[9] The mechanism in eq 1 predicts an

$$I_p = (2.69 \times 10^5)AC_0D^{1/2}n^{3/2}\nu^{1/2} \quad (2)$$

unusual dependence of the peak current on $\nu^{1/2}$. At rapid scan rates where the cleavage reaction does not occur before reoxidation, peak A should represent a one-electron transfer ($n = 1$). On the other hand, at slow scan rates, the cleavage reaction will occur rapidly relative to the scan rate, and the TQ monomer thus generated will also undergo reduction. The latter would make $n = 2$. Therefore, the mechanism in eq 1 predicts that a plot of I_p vs. $\nu^{1/2}$ will not be linear, but will have a slope that depends on the scan rate. The results of such an analysis are diagrammed in Figure 2. The experimental curve does, in fact shows linear behavior at slow scan rates (<400 mV/s). At high scan rates the dependence is also linear, but with a smaller slope. Between 400 and 800 mV/s there is a transition between the two limiting cases. This experiment demonstrates that some new electroactive species (TQ) is being generated upon reduction of TQ_2.

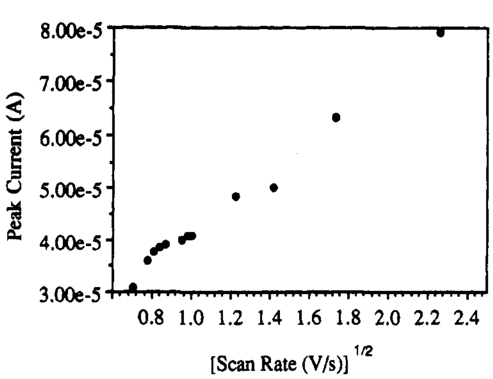

Figure 2. Dependence of the peak current (I_p) for the reduction of TQ_2 in CH_3CN/(0.1 M Bu_4NPF_6) (e.g., peak A in Figure 1) on the square root of the scan rate ($\nu^{1/2}$).

Several alternative assignments for this behavior are excluded based on these experiments. Assignment of the C/D peaks to the second reduction of TQ_2 is excluded. Such a process would most likely occur at more negative potentials than the A/B. If it did occur at less negative potentials, a two-electron wave at the A/B potential would result. The fact that it occurs at more positive potentials, and then only at the lower scan rates, implies that some sort of chemical reaction occurs subsequent to the reduction of TQ_2. A second alternative is that peaks C and D correspond to the protonated forms of $TQ_2^{\bullet-}$ and TQ. In that case, these peaks would increase at the expense of A and B as proton donors (H_2O) are added to the medium. This is not observed.

Tanko[10] and Tanner[11] have shown that radical anions of substituted cyclopropanes can undergo slow, reversible ring-opening. This suggested that peak C might possibly correspond to oxidation of distonic anion radical 1. The oxidation would generate a 1,4-diradical which would either cleave to yield two neutral monomers (resulting in peak D) or close to regenerate the neutral dimer, TQ_2.[12] In this case, peak A would represent a one-electron process at all scan rates. The scan rate dependence of the peak current (Figure 2) excludes this alternative. These preliminary results do not, however, preclude the intermediacy of 1. It is possible that this species is formed in the rate-determining step or that there is a rapid preequilibrium between $TQ_2^{\bullet-}$ and 1.

These studies provide insight into the structural features which control anion radical cleavage of cyclobutanes. $TQ_2^{\bullet-}$ splits ca. 10^6 times more slowly[13] than thymine dimer anion radicals. Bond breaking occurs when the added electron populates the antibonding orbital of the bond to be cleaved.[14] This would be determined by overlap of the LUMO of the functional group being reduced (enedione

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[13] The rate constant for cleavage of $TQ_2^{\bullet-}$ of 3.0 s^{-1} (CH_3CN) was estimated by comparison of its cyclic voltammogram to a digitally simulated voltammogram (see ref 9a). In THF, cleavage is noticeably slower. A more detailed kinetic analysis, discussion of solvent effects, etc. will be presented in the full paper.

or imido) with the C–C antibonding orbital, and their relative energies. The LUMO energies are related to the one-electron reduction potentials of the cyclobutanes. The reduction potential for thymine dimers has been estimated at −2600 mV based on fluorescence quenching measurements.[15] This is considerably more negative than the value of −1360 mV for TQ_2. In a series of similar cyclobutane derivatives, we would expect the cleavage rate to increase as the reduction potential becomes more negative.[16] A more systematic evaluation of this relationship will be possible after further examples of the reaction are discovered.

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