O-Neophyl-type 1,2-phenyl rearrangement initiated by electron transfer: development of kinetic probes of dissociative electron transfer

Robert L. Donkers, Joseph Tse and Mark S. Workentin*

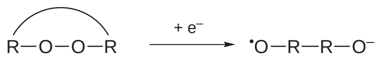
Department of Chemistry, The University of Western Ontario, London, ON, Canada N6A 5B7.
E-mail: mworkent@julian.uwo.ca

Received (in Corvallis, OR, USA) 7th October 1998, Accepted 18th November 1998

The first example of an O-neophyl-type rearrangement in a distonic radical anion was found in the electron transfer induced dissociative reduction of 9,10-diphenyl-9,10-epidioxyanthracene.

Electron transfer (ET) to endoperoxides and peroxides results in the cleavage of the weak oxygen–oxygen (O–O) bond.[1–5] This process proceeds in peroxides and endoperoxides generally by a dissociative ET mechanism,[1–6] in which ET and O–O bond fragmentation are concerted [eqn. (1) or (2)]. Only in the case of *tert*-butyl-*p*-cyanoperbenzoate is there evidence for a transition to a stepwise mechanism with formation of the intermediate radical anion.[5] Such mechanistic studies are important because electron transfer processes of peroxides and endoperoxides play a key role in their activity in chemical and biological systems.[7,8] For example, Fe^{II}-promoted ET reduction of the O–O bond in the antimalarial endoperoxide artemisinin and its semi-synthetic derivatives has recently been shown to be the key step in its antimalarial activity.[9,10] In the cases studied to date using direct electrochemical methods, the alkoxy radical fragment produced in the dissociative reduction (R–O$^\cdot$ for acyclic peroxides or $^\cdot$O–R–R–O$^-$ for endoperoxides) is reduced in a second ET [eqn. (3) or (4)]; *i.e.* no reactivity resulting from the alkoxyl radical fragment is observed.[1–5] Since the initial O–O bond reduction is dissociative, the alkoxyl radical fragment is generated at the electrode that is at a potential more negative than the reduction potential of the R–O$^\cdot$ fragment. Therefore, the alkoxyl radical is reduced spontaneously because of the large driving force. Here we report the first observed[11] reactivity from the alkoxyl radical in the $^\cdot$O–R–R–O$^-$ distonic radical anion formed in a heterogenous dissociative ET, namely a 1,2-phenyl migration (O-neophyl rearrangement). This O-neophyl-type rearrangement of a phenyl group to the alkoxyl radical fragment occurs in the distonic radical anion formed by electrochemical single ET to the O–O bond in the endoperoxide 9,10-diphenyl-9,10-epidioxyanthracene (**DPA-O$_2$**). In addition to being the first example of this type of reaction, this rearrangement occurs at the expense of the reduction of the alkoxyl radical portion of the distonic radical anion [eqn. (4)]. This suggests that systems such as these can be developed as kinetic probes of the rate of the second heterogeneous ET [eqn. (3) and (4)].

$$\mathrm{R{-}O{-}O{-}R} \xrightarrow{+\,e^-} \mathrm{R{-}O^\bullet + R{-}O^-} \qquad (1)$$



$$\mathrm{R{-}O{-}O{-}R} \xrightarrow{+\,e^-} \mathrm{{}^\bullet O{-}R{-}R{-}O^-} \qquad (2)$$

$$\mathrm{R{-}O^\bullet + R{-}O^-} \xrightarrow{+\,e^-} \mathrm{2R{-}O^-} \qquad (3)$$

$$\mathrm{{}^\bullet O{-}R{-}R{-}O^-} \xrightarrow{+\,e^-} \mathrm{{}^-O{-}R{-}R{-}O^-} \qquad (4)$$

Electrochemical reduction of **DPA-O$_2$** was investigated in MeCN and DMF solutions containing 0.1 M tetraethylammonium perchlorate (TEAP) using cyclic voltammetry (CV).[12] In MeCN, **DPA-O$_2$** is reduced with a peak potential (E_p) of -1.12 V *vs.* SCE at a scan rate (v) of 0.1 V s^{-1} and the E_p shifts to more negative potentials with increasing scan rate. The irreversible reduction wave is very broad, with a peak width ($E_p - E_{p/2}$) of 148 mV (at 0.1 V s^{-1}) and α values[13] of 0.32, 0.27, 0.23 and 0.21 at 0.1, 1, 5 and 10 V s^{-1}. These voltammetric characteristics are consistent with the reduction of **DPA-O$_2$** being dissociative.[6] A representative cyclic voltammogram is shown in Fig. 1(*a*). Following the dissociative reduction wave there is a second reversible redox couple at a more negative potential. The reduction wave of this couple[14a] is not well-defined until the potential is scanned to more negative values. This feature and the reversibility of this 1 F mol^{-1} process[14b] are illustrated in Fig. 1(*b*). This reversible reduction at -1.804 V *vs.* SCE was identified as 9-phenoxy-10-phenylanthracene (**PPA**) by product isolation and characterization, and by its standard reduction potential ($E°$). The amount of **PPA** formed in the CV experiment depends on the scan rate and the time the potential is held at values more negative than *ca.* -1.9 V. Based on peak current measurements (i_p) the formation of **PPA** is quantitative on the cyclic voltammetry timescale at very slow scan rates and when the potential is held at the negative potentials.[15] Also observed in the CV on the return cycle are two weak oxidation waves; these disappear on addition of a weak acid (see Fig. 1) and are assigned to electrogenerated basic intermediates. In no case was there evidence for direct reduction of the distonic radical anion leading to the corresponding 9,10-diol, **DPA-(OH)$_2$** (Path **A** in Scheme 1), contrary to that observed in all other peroxide/endoperoxide systems studied to date.[1–5]

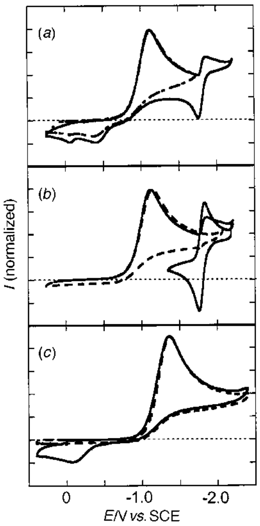
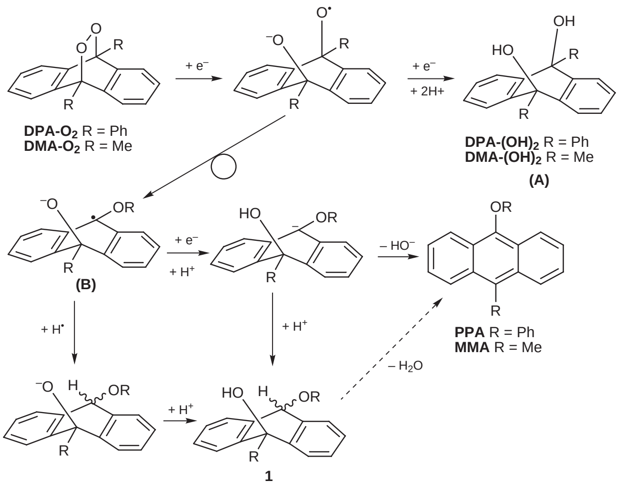


Fig. 1 (*a*) Cyclic voltammogram showing the reduction of a 2 mM solution of **DPA-O$_2$** in 0.1 M TEAP/MeCN at 0.2 V s^{-1}. (*b*) CV as in (*a*) where the potential was held at the negative potential limit for 30 s prior to the positive scan. The CV shown in the dashed line is that measured after the addition of 5 equiv. of 2,2,2-trifluorethanol. (*c*) Cyclic voltammogram showing the reduction of a 2.8 mM solution of **DMA-O$_2$** in 0.1 M TEAP/MeCN at 0.1 V s^{-1} both in the presence (solid line) and the absence (dashed line) of 2,2,2-trifluoroethanol.



Scheme 1

In contrast, reduction of 9,10-dimethyl-9,10-epidioxyanthracene (**DMA-O_2**) generates the corresponding 9,10-diol [**DMA-$(OH)_2$**] quantitatively *via* a two-electron (2 F mol^{-1}) reduction (Path **A** in Scheme 1). No evidence for 9-methoxy-10-methylanthracene (**MMA**) was found. Other voltammetric characteristics are similar to **DPA-O_2**: $E_p = -1.35$ V *vs.* SCE at 0.1 V s^{-1}, a peak width ($E_p - E_{p/2}$) of 153 mV (at 0.1 V s^{-1}) yielding α values of 0.31, 0.27 and 0.25 at 0.1, 1 and 10 V s^{-1}. Since this is a two electron process the shift of E_p to more negative potentials by 113 mV/(log v) gives an average α value of 0.25.

We rationalize formation of **PPA** in the reduction of **DPA-O_2** by an O-neophyl-type rearrangement from the initially formed distonic radical anion (path **B** in Scheme 1); specifically the distonic radical anion undergoes a 1,2-phenyl migration to the alkoxyl radical center to generate the carbon-centered radical intermediate. At the potential where **DPA-O_2** is reduced ($E_p = -1.12$ V *vs.* SCE) the resulting diarylphenoxymethyl radical is not expected to be reduced.[16] This intermediate can be reduced at more negative potentials and eventually lead to **PPA** *via* aromatization with loss of OH^-. This result is consistent with the CV results and was verified by the constant potential electrolysis studies. Electrolysis at −1.2 V does not result in formation of **PPA**; instead it generates *via* a 1 F mol^{-1} process a product that forms **PPA** quantitatively after work-up of the electrolysis mixture. However, if the electrolysis is performed at more negative potentials (−1.6 V) **PPA** is formed quantitatively consuming 2 F mol^{-1}. Likewise if the electrolyses are performed in the presence of a weak acid like 2,2,2-trifluorethanol or acetanilide, **PPA** is not the initial product, but it is the only product isolated after work-up. We suggest that in these latter experiments **1** is formed by trapping the intermediate formed after the O-neophyl rearrangement. No **DPA-$(OH)_2$**, which is stable to the work-up conditions, is isolated.

The O-neophyl rearrangement occurs exclusively; no diol, which would be generated on reduction corresponding to eqn. (4), is observed. Thus, the rearrangement must occur with a rate faster than the rate of the heterogeneous ET reduction of the alkoxyl radical formed on the dissociative reduction. The reduction potential of $Ph_3C–O^\cdot$ ($E^\circ_{Ph_3CO^\cdot/Ph_3CO^-}$) is −0.03 V *vs.* SCE;[4] thus the driving force for reduction of the alkoxyl radical at −1.2 V is favorable by at least 23 kcal mol^{-1}. By analogy to the rate constant reported by Falvey *et al.* for the rearrangement of the triphenylmethoxyl radical to α-phenoxydiphenylmethyl radical we expect the O-neophyl rearrangement to be occurring with a rate constant in the order of 5×10^{10} s^{-1} or greater.[17] Thus, the rate of the second ET cannot compete with the O-neophyl rearrangement. This puts an upper timescale by which to compare the rate of the second heterogenous ET. Similar O-neophyl rearrangements were not reported during the electrochemical reduction of $Ph_3CO–OCPh_3$ or $Ph_3CO–OBu^t$,[4] suggesting that there may be a stereoelectronic effect on the rearrangement in the **DPA-O_2** system.

In the reduction of **DMA-O_2** the corresponding 1,2-methyl shift or β-scission does not compete with reduction of the distonic radical anion. Although the β-scission reaction is not known for $Ph_2MeCO^\cdot$ the rate constant of the 1,2-methyl shift rate is estimated to be 4.4×10^6 s^{-1}.[17] This provides a lower rate limit to compare the second heterogenous ET.

Observation of this O-neophyl rearrangement in the reduction of **DPA-O_2** may provide a method to quantify the partitioning ratio (if any) between the charge and spin in the distonic radical anions formed on reduction of unsymmetrically substituted endoperoxides (for example, 9-methyl-10-phenyl-9,10-epidioxyanthracene). Studies of this type are currently in progress. Also in progress are studies addressing the generality of this type of rearrangement on the reduction of other polycyclic aromatic endoperoxides and other aryl substituted endoperoxides, in an attempt to provide ‘clock’ reactions for secondary reduction of distonic radical anions (and its implications on the theory of dissociative ET).

This work is supported financially by NSERC and UWO.

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12 Electrochemical experiments were performed using standard equipment and electrodes as described in ref. 1. All potentials were calibrated internally to ferrocene ($E^\circ_{Fc^+/Fc}$ is 0.449 and 0.475 *vs.* SCE in MeCN and DMF, respectively). Data in DMF is similar and will be reported in the full account of this work.

13 The transfer coefficient (or symmetry factor) α is defined as $\partial\Delta G^\ddagger/\partial\Delta G^\circ$, where $\Delta G^\ddagger$ is the free energy of activation and ΔG° is the free energy of the ET.

14 (*a*) The reduction of **DPA-O_2** is a 1 F mol^{-1} process except under the conditions indicated later. Full details including simulations will be reported separately. (*b*) Determined by comparison of the peak current (i_p) of PPA formed in an electrolysis with that measured with a known concentration of an authentic sample of **PPA**.

15 At higher scan rates the amount of **PPA** formed in the CV is less than quantitative; its presence by CV is absent at scan rates higher than 75 V s^{-1}. In product studies the amount of product derived from the O-neophyl rearrangement is always quantitative. This may be due to a rate limiting aromatization.

16 The reduction potential of the triphenylmethyl radical is at least −1.2V *vs.* SCE and that of tritolylmethyl radical is −1.36 V *vs.* SCE (S. Bank, C. Ehrlich and J. A. Zubieta, *J. Org. Chem.*, 1979, **44**, 1454).

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Communication 8/07795I