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Dissociative Electron Transfer to Biologically Relevant Bicyclic Endoperoxides. Determination of Thermochemical Parameters

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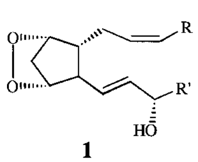
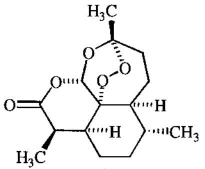
Endoperoxides are important chemical intermediates in the activity of a number of biologically significant substances.[1] Examples include prostaglandin endoperoxide (**1**), important in the biosynthesis of a variety of prostanoids,[2] and the potent antimalarial compound artemisinin (**2**) and its derivatives.[3,4] A key step in the mechanism of action in the antimalarial endoperoxides is likely an electron transfer leading to cleavage of the endoperoxide bond generating oxygen-centered radical intermediates.[5,6] This has also been suggested to be an important step in the prostaglandin endoperoxide bioconversion.[7] Proper consideration of the role of an electron transfer (ET) in the possible modes of action in these systems requires knowledge of the driving force for ET between the donor and endoperoxide, which itself requires accurate values of the reduction potentials of the latter. Reduction of the O−O bond is expected to be dissociative, where bond fragmentation is concerted with electron uptake.[8,9] The standard potential for the dissociative reduction is not determined easily using simple electrochemical methods since the direct reduction is subject to a large overpotential due to a slow heterogeneous ET.[9−12] As a result, reduction potentials measured from cyclic voltammetry are not themselves an accurate indication of the standard potential and cannot be used directly with the oxidation potential of donors to decide whether a particular ET will be feasible under physiological conditions.[13] In such circumstances, thermochemical cycles are often used to estimate the standard reduction potential.[14] Unlike acyclic peroxides, where thermochemical values are available for these calculations, the necessary values are not generally available for endoperoxides due to the complexities of their reactions, making assignment of activation parameters ambiguous.[1]



1



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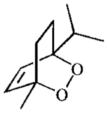
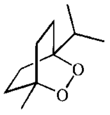


ASC



DASC

In this paper, we report previously unavailable values of the standard reduction potentials ($E^\circ_{\rm diss}$) for two bicyclic endoperoxides, ascaridole (**ASC**) and dihydroascaridole (**DASC**), in aprotic media. These were determined by examining the kinetics of the homogeneous reduction of these endoperoxides as a function of the driving force of ET using a number of radical anion electron donors. **ASC** and **DASC** were chosen as convenient models of the bridged bicyclic endoperoxides found in systems such as **1** and **2**. Data analysis allows estimates of other thermochemical quantities, including bond dissociation free energies. Furthermore, these endoperoxides provide interesting cases for studying and testing novel aspects of the theory of dissociative ET,[10−12] since unlike previous examples the leaving anion remains in the same molecule leading to an unconventional (distonic[15]) radical anion.

Direct voltammetric reduction[16] of **ASC** and **DASC**[17] in acetonitrile (MeCN) and *N*,*N*-dimethylformamide (DMF) exhibits a single broad, irreversible cathodic wave. Peak potentials (E_p) in MeCN are −1.85 and −1.90 V vs SCE at 0.1 V s^{-1}, respectively.[18] Irreversible anodic peaks, due to products of the reduction, are also observed at −0.32 and −0.41 V. Addition of a nonnucleophilic acid does not effect either the peak current or the shape of the cathodic wave but causes the anodic peaks to disappear suggesting that they are due to the alkoxides or other electrogenerated bases. Upon increasing the potential scan rate, ν, the E_p shifts toward more negative values and broadens. From the experimental dE_p/d log ν plots the value of the transfer coefficient, α, was calculated to be 0.23.[19] The transfer coefficient (or symmetry factor), α, reflects how the free energy of activation of ET (eq 1) responds to the driving force and is defined as $\partial\Delta G^\ddagger/\partial\Delta G^\circ_{\rm ET}$, where $\Delta G^\ddagger$ is the free energy of activation and $\Delta G^\circ_{\rm ET}$ is the free energy of reaction. Similar values of α were also obtained from the peak width ($\Delta E_{p/2}$);[19,20] for example, α is independent of solvent and determined to be 0.27 and 0.24 at 0.1 and 1 V/s, for both **ASC** and **DASC**, suggesting a potential dependence of α.[9] Controlled potential electrolysis leads to the consumption of 2 F/mol in both MeCN and DMF in the presence and absence of acid. Analysis of the voltammetric behavior and the products from the controlled potential experiments is consistent with the dissociative reduction of the O−O bond by the overall

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[1] (a) Clennan, E. L.; Foote, C. S. In *Organic Peroxides*; Ando, W., Ed.; John Wiley & Sons, Ltd.: Chichester, England, 1992; Chapter 6, pp 225−318. (b) *Active Oxygen in Chemistry*; Search Series Vol. 2.; Foote, C. S., Valentine, J. S., Greenberg, A., Liebman, J. F., Eds.; Blackie Academic and Professional: New York, 1995. (c) *Active Oxygen in Biochemistry*; Search Series Vol. 3.; Foote, C. S., Valentine, J. S., Greenberg, A., Liebman, J. F., Eds.; Blackie Academic and Professional: New York, 1995.

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[3] Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73−79.

[4] Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. *Microbiol. Rev.* **1996**, *60*, 301−315.

[5] (a) Haynes, R. K.; Vonwiller, S. C. *Tetrahedron Lett.* **1996**, *37*, 253−256. (b) Haynes, R. K.; Vonwiller, S. C. *Tetrahedron Lett.* **1996**, *37*, 257−260. (c) Jefford, C. W.; Vicente, M. G. H.; Jacquier, Y.; Favarger, F.; Mareda, J.; Millasson-Schmidt, P.; Brunner, G.; Burger, U. *Helv. Chim. Acta* **1996**, *79*, 1475−1487.

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[9] Antonello, S.; Musumeci, M.; Wayner, D. D. M.; Maran, F., *J. Am. Chem. Soc.* **1997**, *119*, 9541−9549. We thank Prof. Maran for an advanced copy of this manuscript.

[10] Savéant, J.-M. In *Advances in Electron Transfer Chemistry*; Mariano, P. S., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 4, pp 53−116, and references therein.

[11] (a) Savéant, J.-M. *J. Am. Chem. Soc.* **1992**, *114*, 10595−10602. (b) Savéant, J.-M. *J. Am. Chem. Soc.* **1987**, *109*, 6788−6795.

[12] Savéant, J.-M. *Acc. Chem. Res.* **1993**, *26*, 455−461.

[13] (a) Jiang, H. L.; Chen, K. X.; Tang, Y.; Chen, J. Z.; Li, Y.; Wang, Q. M.; Ji, R. Y.; Zhuang, Q. K. *Ind. J. Chem.* **1997**, *36B*, 154−160. (b) Zhang, F.; Gosser, D. K., Jr.; Meshnick, S. R. *Biochem. Pharmacol.* **1992**, *43*, 1805−1809.

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[15] A distonic radical anion is one in which the charge and radical sites are separated.

[16] Electrochemical experiments were performed in both MeCN and DMF containing 0.1 M tetraethylammonium perchlorate at 25 °C under argon and using a glassy carbon working electrode. Conventional electrochemical instrumentation (EGG PARC 283) was employed. All potentials were calibrated internally to ferrocene which was then calibrated against SCE ($E^\circ_{\rm Fc^+/Fc}$ is 0.449 and 0.470 vs SCE in MeCN and DMF, respectively.

[17] **ASC** and **DASC** were prepared and purified using known procedures: (a) Schenck, G. O. *Angew. Chem.* **1952**, *64*, 12−23. (b) Adam, W.; Eggelte, H. J. *J. Org. Chem.* **1977**, *42*, 3987−3988. *CAUTION:* Peroxides are potentially explosive. Handle with care.

[18] In DMF, the peak potentials for **ASC** and **DASC** are −1.86 and −1.91 V, respectively, at 0.1 V/s.

[19] Bard, A. J.; Faulkner, L. R. *Electrochemical Methods, Fundamentals and Applications*; Wiley: New York, 1980.

[20] From the equation $\alpha = 1.857(RT/F)\Delta E_{p/2}$, where $\Delta E_{p/2}$ is defined as the difference between the potential at half-peak height and E_p.

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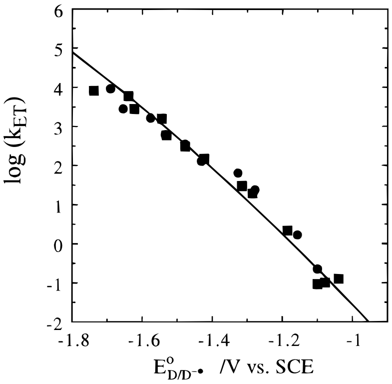
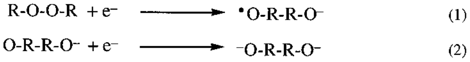


Figure 1. Plot showing the variation in log(k_{ET}) for the homogeneous electron-transfer reaction of a variety of radical anion donors ($D^{\bullet-}$) to **DASC** versus the standard reduction potential of the donor, $E^\circ_{D/D^{\bullet-}}$. Data shown is that for **DASC** in 0.1 M TEAP and DMF (■) and MeCN(●).

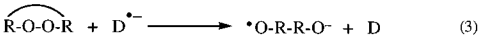
2-electron process according to eqs 1 and 2.[21]



$$\text{R-O-O-R} + e^- \longrightarrow {}^{\bullet}\text{O-R-R-O}^- \qquad (1)$$

$$ {}^{\bullet}\text{O-R-R-O}^- + e^- \longrightarrow {}^-\text{O-R-R-O}^- \qquad (2)$$

The reduction of the endoperoxides by outer sphere homogeneous electron-transfer mediators was studied using an extensive series of electrogenerated donor radical anions ($D^{\bullet-}$), according to eq 3. The experiments involved using both the method of homogeneous redox catalysis[22] and other homogeneous kinetic methods to extend the studies to slower reactions.[23] In the former,



$$\text{R-O-O-R} + D^{\bullet-} \longrightarrow {}^{\bullet}\text{O-R-R-O}^- + D \qquad (3)$$

the catalytic increase in current for the reduction of the donors (they are regenerated in the ET) in the presence of varying concentrations of **ASC** or **DASC** and at different ν was measured and compared to that obtained by simulation to obtain k_{ET}.[24] In none of the cases is there evidence for any competing reactions between the $D^{\bullet-}$ and endoperoxides.

A plot of log(k_{ET}) versus the standard potential of the ET donors ($E^\circ_{D/D^{\bullet-}}$) for reaction with **DASC** in both DMF and MeCN is shown in Figure 1.[25] The figure illustrates the parabolic activation−driving force relationship predicted[10−12] for these dissociative ETs.[26] A similar plot was obtained for **ASC**.

The resulting log(k_{ET}) vs $E^\circ_{D/D^{\bullet-}}$ can be related to the transfer coefficient using eq 4. Thus, derivatization of the curve obtained by a quadratic fit to the data for **ASC** and **DASC**

$$\alpha = -(2.303RT/F)\ \mathrm{d}(\log k)/\mathrm{d}E \qquad (4)$$

gives the equations $\alpha = 1.58 + 0.834\mathrm{E}$ and $\alpha = 1.25 + 0.585\mathrm{E}$, respectively. A value of $\alpha = 0.5$ corresponds to the dissociative reduction potentials E°_{diss};[10] therefore, using the above equations values of −1.29 and −1.28 V are obtained for the dissociative reduction potential of **ASC** and **DASC**, respectively. The E°_{diss} values agree with those determined independently by convolution analysis.[9,27,28] These values indicate that both **ASC** and **DASC** were reduced heterogeneously with overpotentials of at least 0.5 V. *Therefore, any thermodynamic significance linked to the observed direct reduction potential for estimating the driving force for a homogeneous ET would have, in fact, been underestimated by at least 12 kcal/mol.* The line shown in Figure 1 was obtained by fitting the data to the general expression for an adiabatic electron transfer (eqs 5 and 6 where $\Delta G^{\ddagger}_0$ is the intrinsic barrier) using the value of E°_{diss} determined above in the determination of ΔG°_{ET} and the typical value of 3×10^{11} s^{-1} for the preexponential term.[8]

$$k_{ET} = Z \exp(-\Delta G^{\ddagger}/RT) \qquad (5)$$

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_0 (1 + \Delta G^\circ_{ET}/\Delta G^{\ddagger}_0)^2 \qquad (6)$$

With the E°_{diss} values determined, the homogeneous ET rate data can be plotted as a function of ΔG°_{ET} ($\Delta G^\circ_{ET} = 23.06(E^\circ_{D/D^{\bullet-}} - E^\circ_{diss})$) and directly compared to the rate constants obtained for reduction of the acyclic di-*tert*-butyl peroxide (**DTBP**).[8] For ET values of similar driving forces, **ASC** and **DASC** are found to react 2 orders of magnitude more rapidly than **DTBP**. This value is expected if one considers a steric effect to ET in **DTBP** due to the alkyl groups shielding the O−O σ^* orbital, where the electron is transferred.[8] This aspect and other novel aspects of our probes pertaining to the theory of dissociative ET developed by Savéant[10] is forthcoming.[28]

Using a simple thermochemical cycle,[14] the E°_{diss} values can further be related to the respective bond dissociation free energies (BDFE) of the endoperoxides. This requires estimates for the reduction of the alkoxy radical like fragment formed in eq 1. Using a reasonable approximation that $E^\circ_{RO^\bullet/RO^-}$ is equal to the standard potential of the tertiary alkoxy radical $E^\circ_{t-BuO^\bullet/t-BuO^-}$,[29] then the BDFE of these two endoperoxides is estimated to be 24 ± 2 kcal/mol. This value is only slightly smaller than the average value derived for the acyclic peroxides.[8,9] For the fragmentation of the endoperoxides, where both fragments involved in the reduction remain in the same molecule, we expect that the entropic term ($T\Delta S$) will be significantly lower than that for the acyclic peroxides, where $T\Delta S$ is estimated to be 6−8 kcal/mol.[9] Therefore, analysis of our data suggests that the bond dissociation enthalpy of these endoperoxides is smaller than **DTBP** and related peroxides by ca. 8−10 kcal mol^{-1}. This type of difference (although not necessarily the magnitude) is expected due to the added strain and eclipsing interactions of the lone pairs on the oxygen.

In summary, we have studied the dissociative reduction of two bicyclic endoperoxides and have been able to determine for the first time values for the standard potential of their reduction that are essential in consideration of the role of ET in the biological systems. These methods are being expanded to estimate the thermochemical properties of other endoperoxides of biological significance, including **2**, which also undergoes a dissociative reduction.[30] This thermochemical data will allow judicious choice of ET agents to study the activity of these endoperoxides in the biological environments.

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Supporting Information Available: Table of kinetic data and donors (1 page, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[21] Bulk electrolyses were carried out under constant potential conditions in a divided cell at both Hg pool and Pt mesh cathodes. In all cases, the corresponding diols were obtained quantitatively.

[22] (a) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; M'Halla, F.; Savéant, J.-M. *Electroanal. Chem.* **1980**, *113*, 19−40. (b) Andrieux, C. P.; Savéant, J.-M. *Electroanal. Chem.* **1986**, *205*, 43−58.

[23] Daasbjerg, K.; Pedersen, S. U.; Lund, H. *Acta Chem. Scand.* **1991**, *45*, 424−430.

[24] Simulation of experimental curves for an overall 2-electron process was performed using the Digisim 2.1 program by Bioanalytical Systems. For the homogeneous redox catalysis experiments, at least 3 concentrations of **ASC** or **DASC** and several sweep rates were used to obtain data. A table listing the donors used and the resulting kinetic data is provided as Supporting Information.

[25] Average of at least two independent experiments. Data corresponding to the slowest reactions that are important in defining the parabolic shape of the plot have been performed more often and with a variety of donors with similar E° to verify the value of the rate constant with donors at that potential.

[26] It has been suggested that such log(k_{ET}) vs E° relationships may be linear. (For example, see: (a) Lund, H.; Daasbjerg, K.; Lund, T.; Pedersen, S. U. *Acc. Chem. Res.* **1995**, *28*, 313−319. (b) Grimshaw, J.; Langan, J. R.; Salmon, G. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1115. (c) Grimshaw, J.; Langan, J. R.; Salmon, G. A. *J. Chem Soc. Faraday Trans.* **1994**, *90*, 75−81. (d) Reference 23.) However, in our case, a linear fit of the data is poor (R = 0.971) with the residuals of this fit suggesting a parabolic relationship.

[27] Imbeaux, J. C.; Savéant, J.-M. *J. Electroanal. Chem.* **1973**, *44*, 169−187.

[28] The results of the convolution analysis of **ASC, DASC**, and other endoperoxides will be published separately.

[29] $E_{t-BuO^\bullet/t-BuO^-} = -0.23$ vs SCE in DMF.[8]

[30] Workentin, M. S.; Donkers, R. L. Submitted.