COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Radical anion chain process initiated by a dissociative electron transfer to a monocyclic endoperoxide.

Donald L. B. Stringle, R. Nevin Campbell and Mark S. Workentin*
Department of Chemistry, The University of Western Ontario, London, ON, Canada.
E-mail: mworkent@uwo.ca; Fax: 519 661 3022; Tel: 519 661 2111 Ext 86319

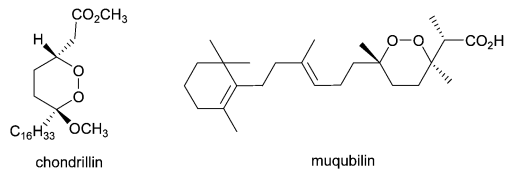
Received (in Corvallis, OR, USA) 17th February 2003, Accepted 13th March 2003
First published as an Advance Article on the web 23rd April 2003

Electron transfer to 3,3,6,6-tetraphenyl-1,2-dioxane results in the cleavage of the oxygen-oxygen bond, generating a distonic radical anion intermediate whose fragmentation initiates an unprecedented radical anion chain process in competition with a second electron transfer.

Monocyclic endoperoxides, compounds containing an oxygen–oxygen (O–O) bond within a cyclic molecular framework, are a common structural moiety of many bioactive marine metabolites that display an array of antitumour, antimicrobial and antiviral activities.[1,2] Examples include, chondrillin and muqubilin (shown below), but many structurally related monocylic endoperoxides, including those with aryl substituents, have since been isolated. The focus of research in this area has been on their isolation and identifying the types of bioactivity and less on how the structure of these compounds brings about their bioactivity. In other naturally occurring endoperoxide systems, electron transfer (ET) to the O–O bond is believed to be critical to their bioactivity,[3] however information regarding electron transfer to endoperoxides in the literature is scarce. Our interest has been in developing an understanding of the factors governing the ET processes of endoperoxides. Earlier studies focused on the ET reduction of alkyl substituted bicyclic endoperoxides serving as models for some biologically relevant endoperoxides.[4] These studies determined that ET is a concerted dissociative process resulting in O–O bond cleavage concomitant with the acceptance of the electron. This results in the formation of a species containing spatially distinct alkoxyl radical and alkoxy anion centres, termed a distonic radical anion (eqn. 1). The alkoxyl radical centre has a reduction potential

$$\text{R-O-O-R} \xrightarrow{e^-} {}^{\bullet}\text{O-R-R-O}^- \xrightarrow[2\ H^+]{e^-} \text{HO-R-R-OH} \qquad (1)$$

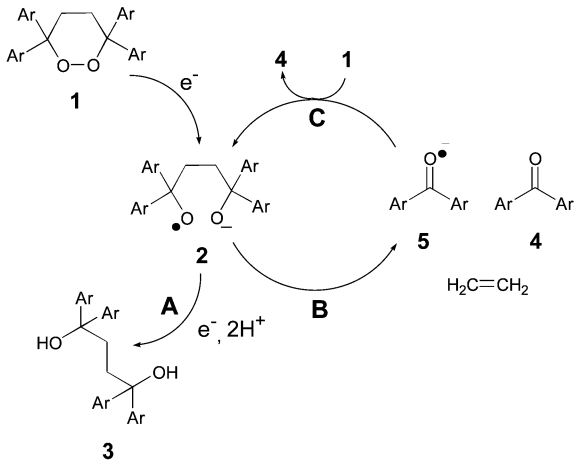
much more positive than that of the starting endoperoxide and thus undergoes a subsequent ET resulting in the ultimate formation of a diol species as illustrated in eqn. 1, similar to ET in other peroxide systems.[5]



chondrillin muqubilin

In the present study we investigated the ET to the monocylic endoperoxide 3,3,6,6-tetraphenyl-1,2-dioxane (**1**, Scheme 1). Besides serving as a model of bioactive monocyclic endoperoxides, **1** also contains phenyl rings that have a dramatic effect on the reactivity of the distonic radical anion providing insight into the mechanistic possibilities of endoperoxides following an ET event. Further, ET to **1** generates a distonic radical anion that fragments in competition with a second ET generating a radical anion that initiates an ET chain process.

The ET chemistry of **1** was studied by electrochemical methods, using cyclic voltammetry (CV) performed at a 3 mm glassy carbon working electrode in 0.1 M tetraethylammonium perchlorate (TEAP) solutions in *N*,*N*-dimethylformamide (DMF). Representative voltammograms are shown in Fig. 1. When scanning cathodically an initial broad peak is observed, irreversible at all scan rates studied (shown as a solid line in Fig. 1a). The relevant CV data are listed in Table 1. The decrease in peak potential to more negative values and increase in the peak breadth with increasing scan rate are consistent with the ET occurring by a concerted dissociative process.[4–6] At low scan rates the tail of this peak is interrupted by an unusual oxidative dip in the current (arrow in dashed curve, Fig. 1). This dip becomes less pronounced at higher scan rates. Following this



Scheme 1 Mechanism of the ET reduction of **1**.

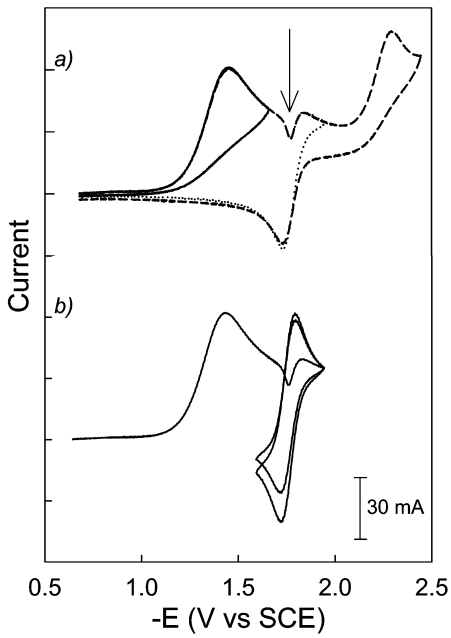


Fig. 1 Cyclic voltammograms showing the reduction of a 2.2 mM solution of **1** in 0.1 M TEAP–DMF (*a*) when switching the potential at −1.59 V (solid), −1.95 V (dotted) and −2.45 V (dashed) and (*b*) CV as in (*a*) now repetitively cycling between −1.55 V to −1.95 V to observe the reversible wave due to benzophenone.

DOI: 10.1039/b301909h

dip are the peaks due to the redox chemistry of the product formed by ET to **1**. The reversibility of the reduction of this product is more evident in Fig 1b where we have used repetitive cycling voltammetry. The product was identified as benzophenone (**4**, Scheme 1) based on its standard reduction potential ($E°_{4/4\cdot-}$) value of −1.77 V *vs* SCE and product studies. From the observed voltammetry, it appears the only electroactive product from the reduction of **1** is **4**. Preparative scale experiments using constant potential electrolysis (CPE) were performed. Benzophenone was identified as a product in all CPE experiments, the other products observed being the corresponding diol (**3**, Scheme 1) and 1,1-diphenylprop-2-en-1-ol (**6**). The crucial observation from these CPE experiments was that the product ratios were dependent on the potential at which the reduction was performed. When reduction was performed at or near the peak potential of the dissociative wave (E_p = −1.5 V) 1.9 F mol^{-1} of charge were consumed, equating to nearly a two electron reduction, consistent with eqn. 1. Work-up and analysis of the cell solution revealed that **3** was produced in nearly quantitative yield, with **4** and a barely detectable amount of **6** as the only other products (3 : 4 = 89 : 11). The result is not particularly surprising given that in a concerted dissociative ET the distonic radical anion is generated very close to the electrode surface and subsequent reduction of the alkoxyl centre, which has a reduction potential over 1 V less negative, is a highly driven process. When the reduction potential is shifted negatively to a value $\leq E°_{4/4\cdot-}$product **4** is favoured over **3** in a ratio of 98 : 2, along with a minor amount of **6**. Most notably, only 0.08 F mol^{-1} of charge were necessary for the complete reduction of **1** at this potential.

To account for these observations we propose a competitive mechanism illustrated in Scheme 1, which includes an unprecedented radical anion chain process. Initially **1** is reduced by a concerted dissociative ET to give the distonic radical anion (**2**). A subsequent ET to **2** (path A) generates a dialkoxy species that upon work-up gives **3**. However, **2** can also undergo a fragmentation process (path B) that produces **4**, ethylene and most importantly the benzophenone radical anion (**5**). Given that the value of $E°_{4/4\cdot-}$ under our conditions is −1.77 V *vs* SCE, and the peak potential of **1** is only −1.43 V *vs* SCE, which is negative of the true standard reduction potential of **1**,[4,5] ET from **5** to **1**(path C) is a strongly exothermic process (ΔG_{ET} > −9.6 kcal mol^{-1}). The differing product ratios are a direct result of the concentration of **5** generated at the electrode under the experimental conditions.

We first examine the case when the electrode potential is negative of $E°_{4/4\cdot-}$. Under these conditions any **4** that is generated by fragmentation of **2** will be reduced at the electrode to give **5**. Because the fragmentation of **2** produces an equivalent of **5**, one fragmentation event results in two equivalents of **5** being produced. If fragmentation of **2** is competitive with its reduction there will be an eventual build up of **5** at the electrode surface. Incoming **1** diffusing toward the electrode then reacts with **5** in a homogeneous ET and is reduced to give **2** and **4**. When **2** is produced away from the electrode it has essentially only one fate; fragmentation. This assertion is evidenced by the reduction of **1** by its addition to a solution of two equivalents of electrochemically generated **5**. The formation of **3** by two successive homogeneous ET was a possibility however, following work-up **4** was the sole product. Thus fragmentation of **2** away from the electrode generates an equivalent of **5** that can subsequently reduce another equivalent of **1**. The resulting radical anion chain process spreads throughout the bulk of the solution allowing for complete reduction without stoichiometric charge consumption. When the electrode potential is positive of $E°_{4/4\cdot-}$, any **5** generated at or near the electrode surface will be oxidised to **4**, thus eliminating the chain propagating species and nullifying the chain process.

Table 1 Data obtained from CV experiments of **1** in 0.1 M TEAP solution in DMF

	ν^b/V sec^{-1}	**1**	**1**/acid[a]
$E_p{}^b$/V	0.1	−1.43	−1.53
	1.0	−1.52	−1.65
$\Delta E_p = (E_p - E_{p/2}{}^b)$/mV	0.1	135	152
	1.0	144	174
$Ip/(\nu)^{1/2b}$/mAs$^{1/2}$ V$^{-1/2}$		54	52
$\alpha = (RT/F)(E_p - E_{p/2})$		0.34	0.29
$\delta E_p/\delta(\log \nu)$/mV		−110	−130

[a] Experiments performed in the presence of a minimum of 10 mM 2,2,2-trifluoroethanol. [b] E_p = peak potential; I_p = peak current; ν = scan rate; $E_{p/2}$ = potential at half-peak current.

Evidence for this mechanism comes from the oxidative dip observed in the voltammetry of **1**. The value of the current is a reflection of the concentration of **1** reaching the electrode to be reduced. The decrease in cathodic current results from a decrease in concentration of **1** at the electrode. The dip occurs just before $E°_{4/4\cdot-}$, the point at which the equilibrium between **4** and **5** at the electrode surface begins to shift in favour of **5**. The increase in **5** coincides with a rapid and dramatic decrease in the concentration of **1** near the electrode surface, indicated by the current decrease in response. This is a strong indication that our proposed radical anion chain mechanism is in operation. Similar current dips have been observed in the voltammetry of $S_{RN}1$ systems,[7] but are an unusual phenomenon that can be taken advantage of in preparative chemistry.

In conclusion we report a unique radical anion chain process that is initiated by a dissociative ET to an endoperoxide. The fragmentation of the distonic radical anion is novel, and few examples of such reactivity from a distonic radical anion exist. Our results demonstrate that the type of reactivity that could follow a single ET reduction to a monocyclic endoperoxide and could have implications on the mechanisms of bioactive marine metabolites. The fragmentation that generates the chain propagating species must be competitive with the reduction of the alkoxyl radical centre under both heterogeneous and homogeneous ET conditions. Thus we can use the rate of the fragmentation of the distonic radical anion as a radical anion clock for determining the rate of ET from various reductants. We are currently pursuing this aspect of the reactivity.

The authors acknowledge the NSERC of Canada, ADF-UWO, PREA, CFI and the ORDCF for financial support. DLBS thanks NSERC for a postgraduate scholarship.

Notes and references

1 D. Casteel, *Nat. Prod. Rep.*, 1992, **9**, 289; D. Casteel, *Nat. Prod. Rep.*, 1999, **16**, 55.
2 S. Sperry, F. A. Valeriote, T. H. Corbett and P. Crews, *J. Nat. Prod.*, 1998, **61**, 241; K. A. El Sayed, M. T. Hamann, N. E. Hashish, W. T. Shier, M. Kelly and A. A. Khan, *J. Nat. Prod.*, 2001, **64**, 522; D. T. A. Youssef, W. Y. Yoshida, M. Kelly and P. J. Scheuer, *J. Nat. Prod.*, 2001, **64**, 1332; Y.-C. Shen, C. V. S. Prakash and Y.-H. Kuo, *J. Nat. Prod.*, 2001, **64**, 324.
3 A. M. Szpilman, E. E. Korshin, R. Hoos, G. H. Posner and M. D. Bachi, *J. Org. Chem.*, 2001, **66**, 6531; J. Cazelles, A. Robert and B. Meunier, *J. Org. Chem.*, 2002, **67**, 609; A. Robert, O. Dechy-Cabaret, J. Cazelles and B. Meunier, *Acc. Chem. Res.*, 2002, **35**, 167.
4 R. L. Donkers, J. Tse and M. S. Workentin, *Chem. Commun.*, 1999, 135; R. L. Donkers and M. S. Workentin, *Chem. Eur. J.*, 2001, **7**, 4012; R. L. Donkers and M. S. Workentin, *J. Phys. Chem. B*, 1998, **102**, 4061.
5 F. Maran, D. D. M. Wayner and M. S. Workentin, *Adv. Phys. Org. Chem.*, 2001, **36**, 85; R. L. Donkers, F. Maran, D. D. M. Wayner and M. S. Workentin, *J. Am. Chem. Soc.*, 1999, **121**, 7239; S. Antonello, F. Formaggio, A. Moretto, C. Toniolo and F. Maran, *J. Am. Chem. Soc.*, 2001, **123**, 9577; S. Antonello, M. Musumeci, D. D. M. Wayner and F. Maran, *J. Am. Chem. Soc.*, 1997, **119**, 9541.
6 J.-M. Savéant, *Adv. Phys. Org. Chem.*, 2000, **35**, 117and references therein.
7 J. Pinson and J.-M. Savéant, *J. Am. Chem. Soc.*, 1978, **100**, 1506; C. Amatore, J. Pinson, J.-M. Savéant and A. Thiebault, *J. Electroanal. Chem.*, 1980, **107**, 75.