

## Reactivity of Superoxide Ion with Halogenonitriles and Dihalocarbons in Aprotic Media

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The reactivity of superoxide ion ( $O_2^{\cdot-}$ ) with halogenated substrates is investigated by cyclic voltammetry and rotated ring-disk electrode method in aprotic solvents. The more positive the reduction potential of the substituted nitrile, the more facile is nucleophilic displacement by  $O_2^{\cdot-}$ . The reaction rates of halogenonitriles with  $O_2^{\cdot-}$  vary according to the leaving-group propensity of halide ( $Br > Cl > F$ ). The relative reaction rates of other substituted nitriles are in the order of electron-withdrawing propensity of the substituent group ( $CN > C(O)NH_2 > Ph \approx CH_2CN$ ). The reaction of  $O_2^{\cdot-}$  with dihalocarbons indicates that five-membered rings can be rapidly formed by the cyclization of substrate and  $O_2^{\cdot-}$ ; and the relative rates of cyclization depend on the number of methylenic carbons [ $Br(CH_2)_nBr$ , [ $n = 1 < 2 < 3 > 4 > 5$ ]]. Mechanisms are proposed for the reaction of  $O_2^{\cdot-}$  with halogenated substrates.

### Introduction

The chemistry and reactivity of superoxide ion ( $O_2^{\cdot-}$ ) interest chemists and biochemists because  $O_2^{\cdot-}$  is a respiratory intermediate<sup>1</sup> and an effective nucleophile in aprotic media.<sup>2</sup> In aprotic media stable solutions of  $O_2^{\cdot-}$  can be prepared by electrochemical<sup>3-7</sup> and chemical<sup>8-12</sup> reduction of dioxygen. Although  $O_2^{\cdot-}$  is a powerful nucleophile in aprotic media, it is deactivated in water because of its large hydration energy ( $\sim 100$  kcal) and rapid hydrolysis and disproportionation.<sup>13,14</sup> The reactivity of  $O_2^{\cdot-}$  with alkyl halides *via* nucleophilic substitution in aprotic solvents was first reported in 1970.<sup>15,16</sup> These and subsequent kinetic studies confirm that the reaction is first order in substrate in aprotic media,<sup>17-19</sup> that the attack by  $O_2^{\cdot-}$  results in inversion of configuration.<sup>20-25</sup> Polyhalogenated aromatic hydrocarbons [e.g., hexachlorobenzene ( $C_6Cl_6$ ) and polychlorobiphenyls (PCB's)] are rapidly degraded by superoxide ion to bicarbonate and halide ions in aprotic solvents.<sup>2,26</sup> Vicinal dibromoalkanes react with  $O_2^{\cdot-}$  to produce products of carbon-carbon bond cleavage.<sup>27</sup> It has proposed that superoxide ion reacts with nitriles by proton abstraction<sup>28</sup> and by nucleophilic addition,<sup>29</sup> and that nitrile reacts with hydroperoxide ion ( $HOO^-$ ) or  $HO^-$  that is generated from the disproportionation of superoxide ion by water.<sup>30,31</sup> The possibility of a nitrile reaction *via* the addition of superoxide ion to its triple bond cannot be fully excluded. In fact,  $NaO_2$  converts aliphatic and aromatic nitriles into the corresponding amides.<sup>20</sup> The rate for the ( $HOO^- + CH_3CN$ ) reaction is faster than that for the ( $HO^- + CH_3CN$ ) reaction;<sup>30</sup>  $ROO^-$  can also convert nitriles to amides.<sup>32</sup> The present study has been directed to the evaluation of the reactivity of electrogenerated  $O_2^{\cdot-}$  with halogenonitriles and dihalocarbons [ $X(CH_2)_nX$ ,  $X = Br$  or  $Cl$ ,  $n = 2-6$ ].

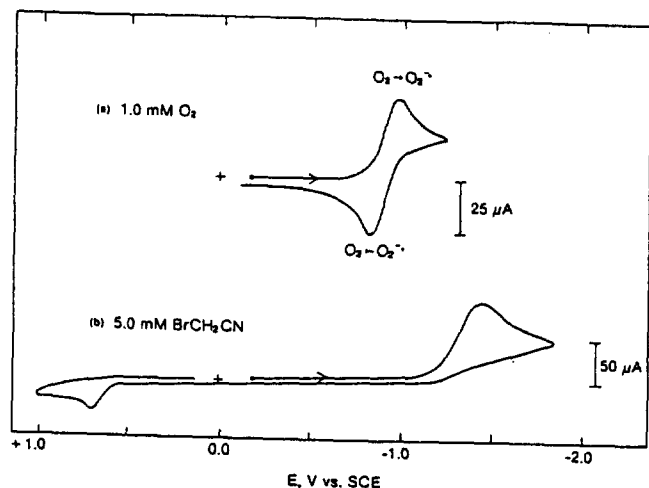
### Experimental

Dimethylformamide (DMF, 0.012%  $H_2O$ ), and acetonitrile (MeCN, 0.002%  $H_2O$ ) (Burdick and Jackson Laboratories, "distilled in glass" grade) were used as aprotic solvents and were kept free of dioxygen under an argon atmosphere. Tetraethylammonium perchlorate [ $TEAP(Et_4NClO_4)$ ] from G. F.

Smith Chemicals was vacuum-dried over  $P_2O_5$  for 24 hours prior to use as the supporting electrolyte (0.1 M TEAP). Bromoacetonitrile ( $BrCH_2CN$ ), 2-bromopropionitrile ( $BrCHMeCN$ ), and malononitrile ( $CNCH_2CN$ ) were used without further purification. All other solvents and chemicals were analytical grade or highest purity available and were used as received.

The cyclic voltammetric measurements were accomplished with a three electrode potentiostat (EG & G Princeton Applied Research model 273). The electrochemical measurements were made with a microcell assembly (10-mL capacity) that was adapted to use a platinum (area, 0.023  $cm^2$ ) or a glassy-carbon (area, 0.06  $cm^2$ ) inlay working electrode, a platinum-wire auxiliary electrode (contained in a glass tube with a medium-porosity glass-frit and filled with a concentrated solution of supporting electrolyte), and a  $Hg/Hg_2SO_4$  (sat'd  $K_2SO_4$ ) (+0.40 V *vs* SCE) was used as the reference electrode. Rotating ring-disk experiments were conducted with a bipotentiostat (EG & G Princeton Applied Research model 366A). A glassy carbon disk/platinum ring electrode was used. The electrochemical cell assembly was treated with  $HNO_3$  overnight and repeatedly soaked in a distilled water bath, and oven-dried at 140  $^\circ C$  for several hours. The electrode surfaces were polished with alumina and Buehler finest quality microcloth immediately prior to each experiment.

The apparent reaction rates for superoxide ion with the various substrates were determined from cyclic voltammetric peak-current measurements<sup>33</sup> and rotating ring-disk electrode method.<sup>38</sup> The reaction stoichiometry of superoxide ion per substrate ( $O_2^{\cdot-}/S$ ) was determined by adding a known amount of substrate to a known excess of  $O_2^{\cdot-}$  in aprotic solvents. The unreacted  $O_2^{\cdot-}$  was assayed by anodic voltammetry. The reaction products from the stoichiometric combination of  $O_2^{\cdot-}$  and substrates were characterized by cyclic voltammetry, UV-VIS spectroscopy, GC, and GC-MS. Halide-ion products were assayed by  $AgNO_3$  titration. For the potentiometric titration of halide ion, 10 mL of distilled water and 0.5 mL of 98% of  $H_2SO_4$  were added to the 10-mL aprotic solution. Argon gas was introduced continuously into the solution during the titration. Cyanate ion in the reaction mixture was quantitatively assayed by a spectrophotometric me-

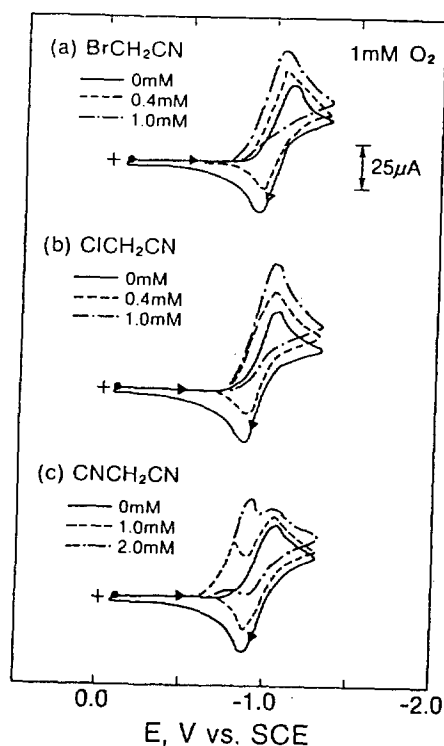


**Figure 1.** Cyclic voltammograms at a glassy carbon electrode (scan rate,  $0.1 \text{ V s}^{-1}$ ) in DMF ( $0.1 \text{ M Et}_4\text{N}(\text{ClO}_4)$ ) of (a)  $1.0 \text{ mM O}_2$  and (b) with  $5.0 \text{ mM BrCH}_2\text{CN}$ .

thod [based on the  $(\text{py})_2(\text{NCO})_2\text{Cu}^{\text{II}}$  complex].<sup>34</sup>

## Results and Discussion

**Reactivity of  $\text{O}_2^-$  with Halogenonitriles.** Figure 1 illustrates the cyclic voltammetry of dioxygen ( $\text{O}_2$ ) [curve a] and of  $\text{BrCH}_2\text{CN}$  [curve b] at a glassy-carbon electrode in dimethylformamide [ $0.1 \text{ M Et}_4\text{N}(\text{ClO}_4)$ ]. Halogenonitriles exhibit a single irreversible two-electron reduction in aprotic solvents (Table 1). Their effect on the electrochemical reduction of  $\text{O}_2$  is illustrated in Figure 2. The cathodic peak current ( $i_{p,c}$ ) for  $\text{O}_2$  increases and the anodic peak current ( $i_{p,a}$ ) for the reverse scan decreases. This is consistent with the effect of alkylhalides in general and is the result of a reaction between  $\text{O}_2^-$  and halogenonitriles. The anodic peaks at  $+0.75 \text{ V}$  and  $+1.00 \text{ V vs SCE}$  after a negative scan to  $-2.5 \text{ V}$  indicate that  $\text{Br}^-$  and  $\text{Cl}^-$ , respectively, are produced from the  $\text{O}_2^-$ /substrate reaction. In MeCN, the halogenonitriles



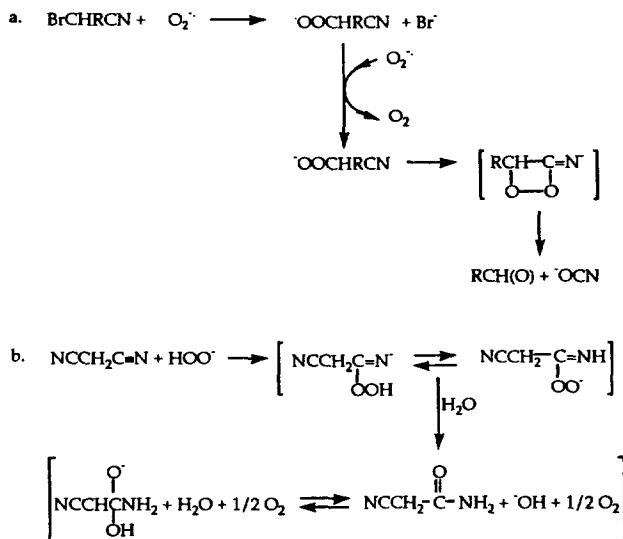
**Figure 2.** Effect of halogenoacetonitriles on the cyclic voltammograms of  $1 \text{ mM O}_2$  at a GC electrode in DMF. (a)  $\text{BrCH}_2\text{CN}$ , (b)  $\text{ClCH}_2\text{CN}$ , and (c)  $\text{NCCH}_2\text{CN}$ .  $0.1 \text{ M Et}_4\text{NClO}_4$ , scan rate  $0.1 \text{ V s}^{-1}$ .

give a single cathodic peak at almost the same potential as in DMF. Controlled-potential reductive electrolysis of  $\text{O}_2$  in the presence of excess  $\text{Br(R)CHCN}$  ( $\text{R}=\text{H}$  or  $\text{Me}$ ) yields  $\text{Br}^-$ ,  $\text{NCO}^-$ , and aldehyde [ $\text{RCH(O)}$ ]. The apparent reaction rates for  $\text{O}_2^-$  with halogenonitriles are determined from cyclic voltammetric peak-current measurements.<sup>33</sup> The reaction stoichiometry of superoxide ion per substrate ( $\text{O}_2^-/\text{S}$ ) was determined by adding a known amount of substrate to a known excess of  $\text{O}_2^-$  in aprotic solvents. The unreacted  $\text{O}_2^-$

**Table 1.** Voltammetric Reduction Potentials ( $E_{p,c}$ ) for Substituted Acetonitriles, and the Stoichiometries and Kinetics for Their Reactions with  $\text{O}_2^-$  in aprotic solvents [ $0.1 \text{ M Et}_4\text{N}(\text{ClO}_4)$ ]

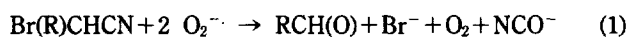
Substrate (S)	$E_{p,c}^a$ V	$\text{O}_2^-$ <sup>b</sup>	Halide <sup>c</sup>	Products <sup>d</sup> per S	$k/[\text{S}]^e, \text{ M}^{-1}\text{s}^{-1}$	
					DMF	MeCN
$\text{FCH}_2\text{CN}$	-2.6	$2 \pm 0.5$	-			
$\text{ClCH}_2\text{CN}$	-1.9	$2 \pm 0.5$	$\text{Cl}^-$	$\text{HCH(O)}$	$1.3 \pm 0.3 \times 10^1$	$2.0 \pm 1.0$
$\text{BrCH}_2\text{CN}$	-1.4	$2 \pm 0.3$	$\text{Br}^-$	$\text{HCH(O)}$	$1.3 \pm 0.3 \times 10^3$	$3.0 \pm 0.5 \times 10^2$
$\text{Br(Me)CHCN}$	-1.5	$2 \pm 0.3$	$\text{Br}^-$	$\text{MeCH(O)}$	$1.5 \pm 0.3 \times 10^3$	$3.6 \pm 0.5 \times 10^2$
$\text{NCCH}_2\text{CN}$	-2.5	$2 \pm 0.4$	-		$1.4 \pm 0.3 \times 10^3$	
$\text{NCCH}_2\text{C(O)NH}_2$	< -3.0	$2 \pm 0.5$	-		$3.5 \pm 0.5 \times 10^2$	$1.0 \pm 0.3 \times 10^1$
$\text{NCCH}_2\text{CH}_2\text{CN}$	-3.0	$2 \pm 0.5$	-		$1.0 \pm 0.3 \times 10^2$	
$\text{PhCH}_2\text{CN}$	-2.9	$2 \pm 0.5$	-		$5.0 \pm 1.0 \times 10^1$	
$\text{C}_6\text{H}_5\text{CN}$	-2.4 <sup>f</sup>	$2 \pm 0.5$	-		$4.9 \pm 1.0 \times 10^1$	

<sup>a</sup>GC electrode; scan rate  $0.1 \text{ V s}^{-1}$ , V vs. SCE. <sup>b</sup> $\text{O}_2^-$  consumed per S. <sup>c</sup>Halide ion released per S which detected by potentiometric titration with aqueous  $\text{AgNO}_3$  ( $0.01 \text{ M}$ ). <sup>d</sup>The reaction products were characterized by ether extraction and capillary-column GC and GC-MS. <sup>e</sup>Pseudo first-order rate constant,  $k$  (normalized to unit substrate concentration  $[\text{S}]$ ;  $[\text{O}_2^-]=1 \text{ mM}$ ). <sup>f</sup>Reversible one-electron couple ( $E_{p,a}$ ,  $-2.3 \text{ V vs SCE}$ ).



Scheme 1.

was assayed by anodic voltammetry. Meanwhile, the apparent pseudo-first order rate constants for  $\text{O}_2^-$  with the halogenonitriles are confirmed by the rotating ring-disk electrode technique;  $\text{O}_2$  is reduced at the disk to  $\text{O}_2^-$  which reacts with substrate, and the unreacted  $\text{O}_2^-$  is oxidized at the ring electrode. The reaction stoichiometry is two electrons ( $2 \text{O}_2^-$ ) per substrate molecule of  $\text{Br(R)CHCN}$  ( $\text{R}=\text{H}$  or  $\text{Me}$ ). The stoichiometries and kinetics for the reactions between  $\text{O}_2^-$  and substituted nitriles ( $\text{RCN}$ ) are summarized in Table 1. The reactivity of  $\text{O}_2^-$  with halogenonitriles in  $\text{MeCN}$  is about one-fourth of that in  $\text{DMF}$ . The overall reaction stoichiometry and products from the combination of  $\text{O}_2^-$  and the bromonitriles [ $\text{Br(R)CHCN}$ ,  $\text{R}=\text{H}$  or  $\text{Me}$ ] in aprotic solvents are represented by Eq. 1 (Table 1).



Because half of the  $\text{Br(R)CHCN}$  remains unreacted from a 1:1  $\text{Br(R)CHCN}/\text{O}_2^-$  combination, the primary step must be rate limiting and followed by a rapid step that consumes a second  $\text{O}_2^-$ . A reasonable reaction sequence (Scheme 1a) is nucleophilic attack of the halocarbon by  $\text{O}_2^-$  with displacement of halide ion as the rate-limiting step. The resulting peroxy radical is reduced by a second  $\text{O}_2^-$  to peroxide ion. The resulting peroxide ion attacks the adjacent cyano group to give a dioxetanimine intermediate *via* intramolecular ring formation, which homolytically dissociates to an aldehyde and a cyanate ion.<sup>27</sup> Neighboring group participations are well known and the related intramolecular four-membered ring formation is  $10^2$ - $10^3$  times as fast as the intermolecular reaction.<sup>36</sup>

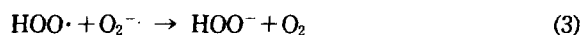
The electrochemical reduction of  $\text{O}_2$  in the presence of  $\text{NCCH}_2\text{CN}$  exhibits a unique prewave in addition to the regular quasi-reversible couple (Figure 2). The new peak increases in height and shifts to more negative potentials with increasing concentrations of  $\text{NCCH}_2\text{CN}$ , and finally merges with the regular  $\text{O}_2/\text{O}_2^-$  couple. The effective  $pK_a'$  values for nitriles and related compounds in  $\text{DMF}$  are summarized in Table 2.<sup>35</sup> Because the reaction rate between  $\text{CNCH}_2\text{CN}$  and  $\text{O}_2^-$  is faster than that of  $\text{PhCH}_2\text{CN}$ , the primary path

**Table 2.** Effective  $pK_a'$  Values for Acidic Substrates in Dimethylformamide

Substrate ( $\text{HA}^+$ , 5 mM)	$E_{ip,c/2}$ , V vs SCE <sup>b</sup>	$pK_a'$
$\text{CNCH}_2\text{CN}$	-1.16	15.6
$\text{CNCH}_2\text{C(O)NH}_2$	-1.61	23.2
$\text{H}_2\text{NC(O)CH}_2\text{C(O)NH}_2$	-1.82	26.8
$\text{PhCH}_2\text{CN}$	-2.10	31.4
$\text{CNCH}_2\text{CH}_2\text{CN}$	-2.15	32.3

<sup>a</sup> For  $\text{HA} + e^- \rightarrow 1/2 \text{H}_2 + \text{A}^-$ ,  $pK_a' = -E_{ip,c/2}/0.0591$ .<sup>35</sup> <sup>b</sup> Measured by cyclic voltammetry at a Pt electrode, scan rate 0.1  $\text{Vs}^{-1}$ .

must be a Brønsted acid-base reaction to give  $\text{CNCHCN}$ , which is stable in the presence of  $\text{O}_2$  and reacts with water to regenerate  $\text{CNCH}_2\text{CN}$ .  $\text{NCCH}_2\text{CN}$  also reacts with  $\text{HOO}^-$  (generated by the disproportionation of  $\text{O}_2^-$  with water) to give  $\text{NCCH}_2\text{C(O)NH}_2$  ( $E_{p,a}$ , +0.14 V vs SCE;  $\epsilon_{251 \text{ nm}} = 15 \text{ mM}^{-1} \text{ s}^{-1}$  for its anion). The new prepeak for  $\text{O}_2$  reduction in the presence of  $\text{NCCH}_2\text{CN}$  (Figure 2) probably is due to the latter's Brønsted acidity towards  $\text{O}_2^-$ . An analogous prepeak for  $\text{O}_2$  reduction is observed in acidified dimethylformamide.<sup>37</sup> Malononitrile ( $pK_a' = 15.6$  in  $\text{DMF}$ ) reacts with  $\text{O}_2^-$  to give  $\text{CNCHCN}$  ( $E_{p,a} = +0.40$  V vs SCE,  $\epsilon_{226 \text{ nm}} = 21 \text{ mM}^{-1} \text{ cm}^{-1}$ ), which is stable in the presence of  $\text{O}_2$



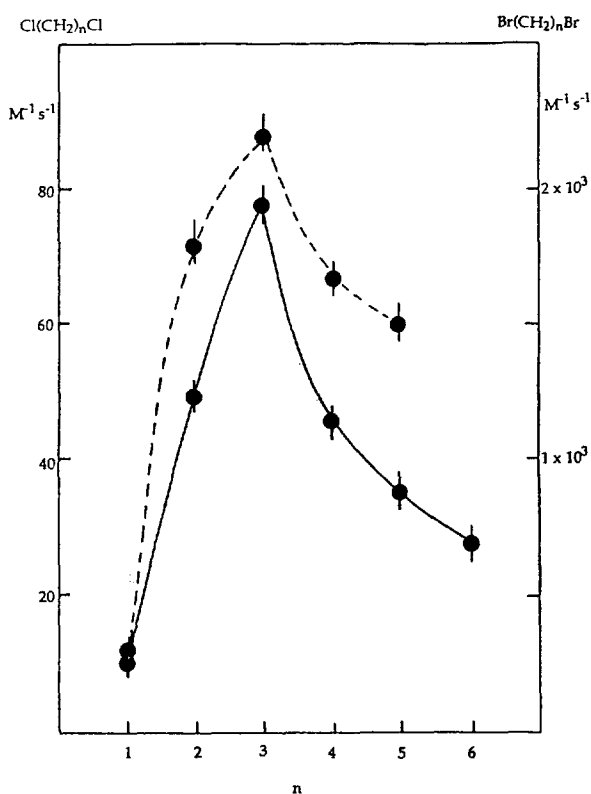
However, the resultant  $\text{HOO}^-$  reacts with  $\text{NCCH}_2\text{CN}$  *via* nucleophilic addition followed by internal proton transfer to produce  $\text{NCCH}_2\text{C(OO}^-)\text{NH}$ . In turn the product hydrolyzes to give  $\text{NCCH}_2\text{C(O)NH}_2$  (mp 122 °C) and  $\text{O}_2$  (Scheme 1b).

The reactivity of  $\text{O}_2^-$  with substituted acetonitriles is affected by the electron-withdrawing and leaving propensities of the substituent group. The more positive the reduction potential of the substituted nitrile, the more facile is nucleophilic displacement by  $\text{O}_2^-$ . Likewise, the greater the electron-withdrawing by the substituents the smaller the  $pK_a'$  of the methylenic hydrogens. The results of Table 1 indicate that the reaction rates of halogenonitriles with  $\text{O}_2^-$  vary according to the leaving-group propensity of halide ( $\text{Br} > \text{Cl} > \text{F}$ ). On the other hand, the relative reaction rates of other substituted nitriles are in the order of electron-withdrawing propensity of the substituent group ( $\text{CN} > \text{C(O)NH}_2 > \text{Ph} \approx \text{CH}_2\text{CN}$ ) *vis-a-vis* the Brønsted basicity of  $\text{O}_2^-$ . The slight decrease of the reaction rate of  $\text{BrCH(Me)CN}$  compared to  $\text{BrCH}_2\text{CN}$  is due to weak electron-donation by the methyl group.

**Reactivity of  $\text{O}_2^-$  with Dihalocarbons.** Superoxide ion readily reacts with substrates that have dihalide groups in aprotic solvents. Table 3 summarizes the reaction stoichiometries and kinetics for the reaction of  $\text{O}_2^-$  with dihalocarbons, and voltammetric reduction potentials ( $E_{p,c}$ ) for dihalocarbons [ $\text{X}(\text{CH}_2)_n\text{X}$ ,  $n=1-6$ ,  $\text{X}=\text{Br}, \text{Cl}$ ] in  $\text{DMF}$ . There is a rough correlation between the apparent second order rate constants for the reaction of  $\text{O}_2^-$  with dihalocarbons and the number of methylene in substrates (Figure 3). The apparent pseudo-first order rate constants for the reaction of the voltammetrically generated  $\text{O}_2^-$  with the various subst-

**Table 3.** Voltammetric Reduction Potentials ( $E_{p,c}$ ) for Dihalocarbons; and the Stoichiometries and Kinetics for Their Reactions with  $O_2^-$  in DMF at 23 °C

Substrates (S)	$E_{p,c}$ , V vs SCE	$k/[S]$ , $M^{-1}s^{-1}$	$O_2^-$ consumed per S	Halide ions released per S
<b>Br(CH<sub>2</sub>)<sub>n</sub>Br</b>				
$n=1$	-2.0	$2.3 \pm 0.5 \times 10^2$	$2 \pm 0.4$	2 Br <sup>-</sup>
$n=2$	-2.1	$1.8 \pm 0.3 \times 10^3$	$2 \pm 0.2$	2 Br <sup>-</sup>
$n=3$	-2.4	$2.2 \pm 0.3 \times 10^3$	$2 \pm 0.2$	2 Br <sup>-</sup>
$n=4$	-2.5	$1.7 \pm 0.3 \times 10^3$	—	—
$n=5$	-2.5	$1.5 \pm 0.3 \times 10^3$	—	—
<b>Cl(CH<sub>2</sub>)<sub>n</sub>Cl</b>				
$n=1$	-2.6	$1.1 \pm 0.2 \times 10^1$	$2 \pm 0.5$	2 Cl <sup>-</sup>
$n=2$	-2.7	$4.7 \pm 1.0 \times 10^1$	$2 \pm 0.2$	2 Cl <sup>-</sup>
$n=3$	-3.0	$7.7 \pm 2.0 \times 10^1$	$2 \pm 0.2$	2 Cl <sup>-</sup>
$n=4$	-3.0	$4.3 \pm 1.0 \times 10^1$	—	—
$n=5$	-3.1	$3.5 \pm 1.0 \times 10^1$	—	—
$n=6$	-3.2	$2.7 \pm 1.0 \times 10^1$	—	—

**Figure 3.** Reaction rates of dihalohydrocarbons with  $O_2^-$  in relation to their carbon number in DMF. (—),  $Cl(CH_2)_nCl$ ; (---),  $Br(CH_2)_nBr$ .

rates are related to the ratio of  $i_{p,a}/i_{p,c}$  for  $O_2$  in the presence of substrate; the normalized pseudo-first order rate constants are tabulated in Table 3. The apparent reaction rates for  $O_2^-$  with the dihalocarbons are determined from cyclic voltammetric peak-current measurements and rotating ring-disk electrode technique. The reaction stoichiometry of superoxide ion per substrate ( $O_2^-/S$ ) was determined by adding

a known amount of substrate to a known excess of  $O_2^-$  in aprotic solvents. The results of Table 3 and Figure 3 indicate that five-membered rings can be rapidly formed by the cyclization of substrate and  $O_2^-$ , and the relative rates of cyclization depend on the number of methylenic carbons  $Br(CH_2)_n$ ,  $Br[n=1<2<3>4>5]$ . Vicinal dibromoalkanes react with  $O_2^-$  to produce products of carbon-carbon bond cleavage.<sup>27</sup> The mechanism proposed for these reactions is a nucleophilic attack on carbon followed by a one-electron reduction of the peroxy radical and nucleophilic displacement on the adjacent carbon to form a dioxetane that subsequently cleaves to form two molecules of aldehyde. Therefore, the reaction of  $O_2^-$  with  $Br(CH_2)_2Br$  as a kind of vicinal dibromo groups yields bromide ion, dioxygen, and two equivalents of formaldehyde. A reasonable mechanism for this cyclization is an initial nucleophilic attack of a bromo carbon by  $O_2^-$  as a rate limiting step, followed by displacement of a bromide ion. A second  $O_2^-$  reduces the peroxy radical to a peroxide ion, which attacks another bromo carbon to displace the second bromide ion to produce a ring intermediate.

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## References

- Knowles, P. F.; Gibson, J. F.; Pick, F. M.; Bray, R. C. *Biochem. J.* **1969**, *111*, 53.
- (a) Sugimoto, H.; Matsumoto, S.; Sawyer, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 8081. (b) Roberts, J. L.; Sawyer, D. T. *J. Am. Chem. Soc.* **1981**, *103*, 712. (c) Sugimoto, H.; Matsumoto, S.; Sawyer, D. T.; Kanofsky, J. R.; Chowdhury, K.; Wilkins, C. L. *J. Am. Chem. Soc.* **1988**, *110*, 5193.
- (a) Sawyer, D. T.; Roberts, J. L., Jr. *J. Electroanal. Chem.* **1966**, *12*, 90. (b) Sawyer, D. T.; Chiericato, G.; Angelis, C. T.; Nanni, E. J.; Tsuchiya, T. *Anal. Chem.* **1982**, *54*, 1720. (c) Sawyer, D. T.; Seo, E. T. *Inorg. Chem.* **1977**, *16*, 499. (d) Cofre', P.; Sawyer, D. T. *Anal. Chem.* **1986**, *58*, 1057.
- Maricle, D. L.; Hodgson, W. G. *Anal. Chem.* **1965**, *37*, 1563.
- Peover, M. E.; White, B. S. *Electrochim. Acta*, **1966**, *11*, 1061.
- Uribe, F. A.; Bard, A. J. *Inorg. Chem.* **1982**, *21*, 3160.
- Lorenzola, T. A.; Lopez, B. A.; Giordano, M. C. *J. Electrochem. Soc.* **1983**, *130*, 1359.
- (a) Roberts, J. L., Jr.; Morrison, M. M.; Sawyer, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 329. (b) Morrison, M. M.; Roberts, J. L., Jr.; Sawyer, D. T. *Inorg. Chem.* **1979**, *18*, 1971. (c) Roberts, J. L., Jr.; Sugimoto, H.; Barrette, W. C., Jr.; Sawyer, D. T. *J. Am. Chem. Soc.* **1985**, *107*, 4556. (d) Srivatsa, G. S.; Sawyer, D. T. *Inorg. Chem.* **1985**, *24*, 1732. (e) Hojo, M.; Sawyer, D. T. *Inorg. Chem.* **1989**, *28*, 1201. (f) Sawyer, D. T.; Roberts, J. L., Jr. *Acc. Chem. Res.* **1988**, *21*, 469. (g) Jeon, S.; Sawyer, D. T. *Inorg. Chem.* **1990**, *29*, 4612.
- Miyazawa, T.; Endo, T.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 5389.
- Patel, K. B.; Willson, R. L. *J. Chem. Soc. Faraday Trans.*

- 1973, 1, 814.
- Holme, B. E.; Land, E. J.; Phillips, G. O. *J. Chem. Soc., Faraday Trans.* 1972, 1, 1992.
  - Saito, I.; Matsuura, T.; Inoue, K. *J. Am. Chem. Soc.* 1983, 105, 3200.
  - Yamadaini, R.; Payzant, J. D.; Kebarle, P. *Can. J. Chem.* 1973, 51, 2507.
  - Pearson, R. G. *J. Am. Chem. Soc.* 1986, 108, 6109.
  - Merritt, M. V.; Sawyer, D. T. *J. Org. Chem.* 1970, 35, 2157.
  - Dietz, R.; Forno, A. E. J.; Larcombe, B. E.; Poever, M. E. *J. Chem. Soc. B* 1970, 816.
  - Sawyer, D. T.; Gibian, M. J. *Tetrahedron*, 1979, 35, 1471.
  - Magno, F.; Seeber, R.; Valcher, S. *J. Electroanal. Chem.* 1977, 83, 131.
  - Gibian, M. J.; Ungermann, T. *J. Org. Chem.* 1976, 41, 2500.
  - San Filippo, J.; Chern, C.-I.; Valentine, J. S. *J. Org. Chem.* 1975, 40, 1678.
  - Johnson, R. A.; Nidy, E. G. *J. Org. Chem.* 1985, 80, 1680.
  - McDonald, R. N.; Chowdhury, A. K. *J. Am. Chem. Soc.* 1985, 107, 4123.
  - Johnson, R. A.; Nidy, E. G.; Merritt, M. V. *J. Am. Chem. Soc.* 1978, 100, 1960.
  - Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* 1975, 3183.
  - Merritt, M. V.; Johnson, R. A. *J. Am. Chem. Soc.* 1977, 99, 3713.
  - (a) Sugimoto, H.; Matsumoto, S.; Sawyer, D. T. *Environ. Sci. Technol.* 1988, 22, 1182. (b) Hojo, M.; Sawyer, D. T. *Chem. Res. Toxicol.* 1989, 2, 193. (c) Sawyer, D. T.; Tsang, P. K. S.; Jeon, S.; Nicholson, M. *Industrial Environmental Chemistry* 1992, 181.
  - Calderwood, T. S.; Sawyer, D. T. *J. Am. Chem. Soc.* 1984, 106, 7185.
  - Tezura, M.; Hamada, H.; Ohkatsu, Y.; Osa, T. *Denki Kagaku* 1970, 44, 19.
  - (a) Sawaki, Y.; Ogada, Y. *Bull. Chem. Soc. Jpn.* 1981, 54, 793. (b) Sawaki, Y.; Ogada, Y. *J. Am. Chem. Soc.* 1977, 99, 6313.
  - Yamaguchi, K.; Calderwood, T. S.; Sawyer, D. T. *Inorg. Chem.* 1986, 25, 1289.
  - Kornblum, N.; Singaram, S. *J. Org. Chem.* 1979, 44, 4227.
  - Gibian, M. J.; Ungermann, T. *J. Am. Chem. Soc.* 1979, 101, 1291.
  - Nicholson, R. S.; Shain, I. *Anal. Chem.* 1964, 36, 706.
  - Martin, E. L.; MacClelland, J. *Anal. Chem.* 1951, 23, 1519.
  - Barrette, W. C., Jr.; Johnson, H. W.; Sawyer, D. T. *Anal. Chem.* 1984, 56, 1890.
  - Richardson, W. H.; Hodge, V. F. *J. Am. Chem. Soc.* 1971, 93, 3997.
  - Chin, D.-H.; Chiericato, G., Jr.; Nanni, E. J., Jr.; Sawyer, D. T. *J. Am. Chem. Soc.* 1982, 104, 1296.
  - Albery, W. J.; Hitchman, M. L. *Ring-Disc Electrodes*; Clarendon Press: Oxford, 1971.

## Synthesis of N-Substituted Isoindolin-1-ones via Palladium-Catalyzed Carbonylative Heterocyclization of *o*-Bromobenzylbromide with Carbon Monoxide and Primary Amines

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A convenient method for the synthesis of N-substituted isoindolin-1-ones is disclosed in palladium(0)-catalyzed heterocyclization of *o*-bromobenzylbromide with carbon monoxide (CO) and primary amines in DMF at 100 °C.

### Introduction

Transition metal-catalyzed carbonylative heterocyclization has been a useful synthetic tool for the formation of a variety of heterocyclic compounds.<sup>1</sup> Thus, the carbonylative cyclization has been effectively applied to the synthesis of isoindolin-1-ones; *i.e.* the cobalt-catalyzed carbonylative cyclization of Schiff's bases with CO,<sup>2</sup> the carbonylation of *o*-palladated benzaldimines and tertiary benzylic amines,<sup>3</sup> the palladium-catalyzed carbonylative cyclization of *N*-benzyl-*o*-bromobenzylamine with CO,<sup>4</sup> and the cobalt-catalyzed carbonylative cyclization of *o*-bromobenzylamines with CO under sunlamp-irradiated phase transfer catalyst (PTC) conditions.<sup>5</sup> On the

other hand, as part of our series of studies on the transition metal-catalyzed heterocyclization,<sup>6</sup> we have now found that *o*-bromobenzylbromide reacts with CO and primary amines in DMF in the presence of a catalytic amount of a palladium compound to afford the corresponding isoindolin-1-ones in good yields. The results presented here lead to the one pot procedure for the synthesis of the N-substituted isoindolin-1-ones from three components, *o*-bromobenzylbromide, primary amines, and CO.

### Results and Discussion

Although Mori<sup>4</sup> and Brunet<sup>5</sup> partly investigated the transi-