Perkin-Markovnikov Type Reaction Initiated with Electrogenerated Superoxide Ion

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The cyclic condensation of active methylene compounds such as diethyl malonate, dimethyl malonate, ethyl acetoacetate, or acetylacetone and dibromoalkanes such as 1,2-dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, 1,5-dibromopentane, 1,6-dibromohexane, 1,3-dibromobutane, or 1,4-dibromopentane with electrogenerated superoxide ion was studied electrochemically in *N,N*-dimethylformamide (DMF) using cyclic voltammetry (CV) and controlled potential macro-electrolysis. The CV shows that electrogenerated superoxide ion reacts with both active methylene compounds and dibromoalkanes in the dissolved oxygen medium. Controlled potential macro-electrolysis of the above components generally yielded cycloalkanes as the main products. In comparison, the chemical method using sodium ethoxide was also carried out. Two reaction mechanisms via the proton abstraction of active methylene compounds with electrogenerated superoxide ion and via the nucleophilic attack of the superoxide ion on dibromoalkanes are presented.

Superoxide ion ($O_2^{\cdot-}$) is not only one of the most important activated forms of molecular oxygen in biological systems but also novel activating reagent for organic synthesis,[1-3] and has recently attracted a great deal of attention of biological and organic chemists. Superoxide ion is produced by the electrochemical reduction of oxygen dissolved in non-aqueous solvent such as pyridine, acetonitrile, or *N,N*-dimethylformamide (DMF) at −0.85 V vs. silver-silver chloride (Ag/AgCl) as shown in Eq. 1.

$$O_2 + e^- \rightarrow O_2^{\cdot-} \qquad (1)$$

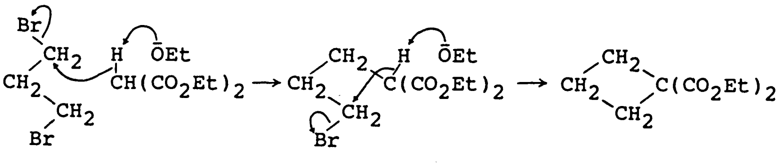
Superoxide ion possesses various reactivities, namely characteristics as a strong base, a nucleophile, an oxidant, a reductant, a free radical, and an electron-transfer agent.[4] In aprotic solvents, superoxide ion acts as an electrogenerated base (EGB),[5] and abstracts a proton of an active methylene group to form a carbanion (EWG-$\bar{C}$H-EWG, EWG: electron-withdrawing group). Electrogenerated superoxide ion has another feature, as a nucleophile;[6] it reacts with alkyl halides to form alkylperoxy radicals (R-OO·), which might be readily reduced further by electrogenerated superoxide ion or by an electron from the electrode to form alkylperoxide ions (R-OO$^-$).

Alkali metal superoxides of potassium and sodium salts are well-known, but their insolubility in the usual organic solvents makes them of little preparative use.[6] Therefore, the reaction of alkali metal superoxides with organic compounds in benzene has been reported by the use of crown ethers in order to solve the problem of their insolubility.[7] On the other hand, the electrochemical method is experimentally more convenient because superoxide ion is continuously generated on the electrode and its solubility is sufficiently high in the presence of the tetraethylammonium cation of supporting electrolyte.[8]

We have investigated the characteristics of the reactivity of electrogenerated superoxide ion toward active methylene compounds and dibromoalkanes, and have reported preliminary results on the reaction of the active methylene compound, such as diethyl malonate, dimethyl malonate, or ethyl acetoacetate and dibromoalkane with electrogenerated superoxide ion.[9] In this paper, we describe in detail the reaction of dibromoalkanes and active methylene compound of acetylacetone as well as malonates and ethyl acetoacetate with electrogenerated superoxide ion in DMF solutions, using cyclic voltammetry and controlled potential macroelectrolysis.

The reaction of this type is well known as Perkin-Markovnikov reaction (Scheme 1).[10,11] The reaction using sodium ethoxide as a base to form an aliphatic ring compound is widely used in organic syntheses. However, the reports on the reaction of this type using electrogenerated superoxide ion as a base, have not previously been published.

After detailed investigation using cyclic voltammetry and macro-electrolysis in DMF, we have concluded that the present reaction system should be considered in terms of the nucleophilic reaction of electrogenerated superoxide ion with dibromoalkanes as frequent as in terms of the proton abstraction of electrogenerated superoxide ion from active methylene compounds. We report here the reaction of active methylene compounds and dibromoalkanes using cyclic



Scheme 1.

voltammetry and macro-electrolysis in DMF, and discuss the results in terms of the basic properties and the nucleophilicity of electrogenerated superoxide ion.

Experimental

Materials. DMF (Guaranteed reagent, Tokyo Kasei) was stored over Molecular Sieves (4A 1/16) for 24 h and then distilled under reduced pressure. Further purification was achieved by passage through a column of activated alumina (ICN Alumina N-Akt. I). Tetraethylammonium perchlorate (TEAP) from Tokyo Kasei (Guaranteed reagent) was dried in vacuo and used as a supporting electrolyte in the electrochemical experiments. The substrates, diethyl malonate (Guaranteed reagent, Nakarai Chemicals), dimethyl malonate (Extra pure reagent, Tokyo Kasei), ethyl acetoacetate (Extra pure reagent, Wako Pure Chemical Industries), and acetylacetone (Guaranteed reagent, Nakarai Chemicals) were purchased commercially and were redistilled. 1,2-Dibromoethane (Extra pure reagent), 1,3-dibromopropane (Extra pure reagent), 1,4-dibromobutane (Guaranteed reagent), 1,5-dibromopentane (Guaranteed reagent), 1,6-dibromohexane (Extra pure reagent), 1,3-dibromobutane (Extra pure reagent), and 1,4-dibromopentane (Extra pure reagent) were also obtained commercially from Tokyo Kasei and were distilled under reduced pressure before use.

Cyclic Voltammety. Cyclic voltammetry was carried out in a DMF solution containing 0.2 M (1 M=1 mol dm^{-3}) TEAP as a supporting electrolyte. A glassy carbon (GC) disk (area ca. 0.71 cm^2) was employed as a working electrode, and a platinum wire was employed as a counter electrode for cyclic voltammetry. The working electrode was polished with a 0.05 μm alumina/water slurry on a felt surface, sonicated in distilled water, throughly washed with acetone, and dried before electrochemical measurements. The cathode potentials were referred to Ag/Ag^+ (0.05 M $AgNO_3$ and 0.1 M TEAP in acetonitrile). Cyclic potential sweeps were generated by a self-made function generator in conjunction with a Hokuto Denko Model HA-305 potentiostat/galvanostat. Cyclic voltammograms were recorded on a Graphtec Model WX1200 X-Y recorder. All electrochemical measurements were carried out at room temperature under a nitrogen atmosphere.

Controlled Potential Macro-Electrolysis. For controlled potential macro-electrolysis, a three compartment cell (H-type cell), in which cathodic and anodic chambers were separated by two fine-porosity sintered-glass frits, was employed with a magnetic stirrer and a reference electrode was put near the cathode. A glassy carbon plate with a surface area of ca. 12.5 cm^2 was used as the cathode, and a platinum plate was used as the anode. An electrolyte solution (0.2 M TEAP) of 60 cm^3 containing two substrates (0.1 M activated methylene compound and 0.1 M dibromoalkane) was placed in the cathodic chamber (25 cm^3), the anodic chamber (25 cm^3), and the middle chamber (10 cm^3). Dry oxygen was bubbled through the cathode. The cathode potential was controlled with a Hokuto Denko Model HA-305 potentiostat/galvanostat. The quantity of electricity passed was measured with a Hokuto Denko Model HF-201 coulomb/amperehour meter. These electrolyses were carried out at room temperature under a nitrogen atmosphere.

Identification of Products and Determination of the Yields. The products of the electrolyses were separated from the catholyte and identified by the following procedure. The catholyte was evaporated in vacuo to remove DMF. The residue was dissolved in water and extracted with diethyl ether. The ether layer was dried over anhydrous sodium sulfate and the ether was removed by distillation under reduced pressure. The resulting liquid was tried to be separated into its components by silica-gel column chromatography using several organic mixed eluents such as hexane–diethyl ether (20:1), but could not be well separated.

Authentic samples of the cycloalkanes were prepared by the ordinary chemical preparative method.[12] The procedure was as follows. In a 100-ml three-necked round bottomed flask, equipped with a reflux condenser capped with a calcium chloride tube, a magnetic stirrer, and a 50-ml pressure-equalizing dropping funnel for addition of prepared 0.02 g·atom sodium ethoxide–ethanol solution, were mixed 0.01 mol each of active methylene compound and dibromoalkane. The mixture was heated to 80 °C and vigorously stirred while the sodium ethoxide–ethanol solution was slowly added into the flask over a 1.5 h period. After the addition was finished, the mixture was refluxed, with continued stirring, for an additional 45 min, and then the ethanol was removed by distillation. The reaction mixture was cooled, and 5 ml of cold water was added. After the sodium halides were completely dissolved, the organic layer was separated and the aqueous layer was extracted with three 10 ml portions of diethyl ether. The combined ether extracts were shaken with 5 ml of saturated NaCl solution, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The identity of the electrochemically prepared cycloalkanes with the respective authentic samples was established by gas chromatography and GC-MS spectroscopy. The main products of electrolyses were detected by using a Shimadzu Model GC-4CM gas chromatograph equipped with 2 m×3 mmϕ column packed with Carbowax 20M, and identified by comparing their retention times with those of authentic samples. Yields of the products were also determined by gas chromatographic analysis. The by-products of electrolyses were identified by using a JEOL Model JMS-DX300 GC-MS spectrograph equipped with 2 m × 3 mmϕ column packed with Silicone OV-101.

Results and Discussion

Cyclic Voltammetry of Active Methylene Compounds and Dibromoalkanes. The cyclic voltammetry of diethyl malonate (**1**), dimethyl malonate (**2**), ethyl acetoacetate (**3**), acetylacetone (**4**), 1,2-dibromoethane (**a**), 1,3-dibromopropane (**b**), 1,4-dibromobutane (**c**), 1,5-dibromopentane (**d**), 1,6-dibromohexane (**e**), 1,3-dibromobutane (**f**), and 1,4-dibromopentane (**g**) was carried out in a 0.2 M TEAP/DMF solution under a nitrogen atmosphere. All the substrates were reduced at more negative potentials than −2.5 V vs. Ag/Ag^+ as shown in Table 1. The compounds **4**, **c**, **d**, **e**, and **g** exhibited prepeaks (E_p^1) at more positive potentials than the main peaks (E_p^2). The cyclic voltammograms of **1**, **a**, and **c** are demonstrated in Fig. 1. The reduction peak of **1** could not

Table 1. Reduction Peak Potentials of Substrates

Compound	E_p^1	E_p^2
Diethyl malonate (**1**)		−3.36
Dimethyl malonate (**2**)		−3.33
Ethyl acetoacetate (**3**)		−2.96
Acetylacetone (**4**)	−2.54	−2.97
1,2-Dibromoethane (**a**)		−2.58
1,3-Dibromopropane (**b**)		−2.87
1,4-Dibromobutane (**c**)	(−2.80)	−3.29
1,5-Dibromopentane (**d**)	(−2.80)	−3.31
1,6-Dibromohexane (**e**)	(−2.80)	−3.39
1,3-Dibromobutane (**f**)		−2.97
1,4-Dibromopentane (**g**)	(−2.80)	−3.24

E/V vs. Ag/Ag$^+$, solvent: DMF, supporting electrolyte: TEAP, working electrode: GC, reference electrode: Ag/Ag$^+$, counter electrode: Pt.

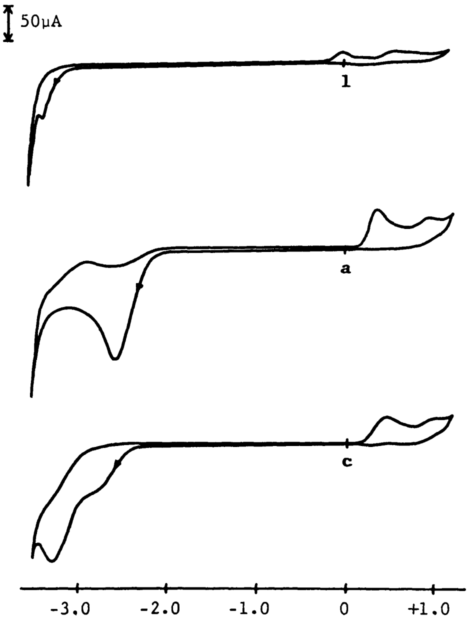


Fig. 1. Cyclic voltammograms of 16 mM **1**, **a**, and **c** in 0.2 M TEAP/DMF at a GC disk electrode. Sweep rate: 0.2 V s^{-1}.

be measured directly because of the deformed CV curve, but the peak potential is estimated to be −3.36 V.

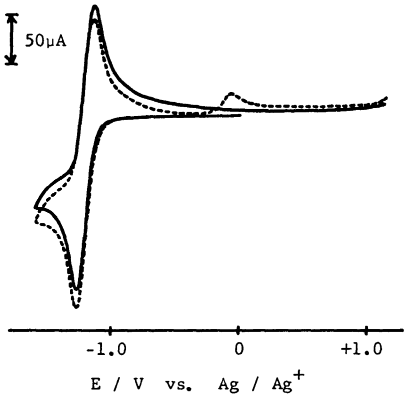


Fig. 2. Cyclic voltammograms of O_2 in the absence (——) and presence (······) of 2 mM **1**. Sweep rate: 0.1 V s^{-1}.

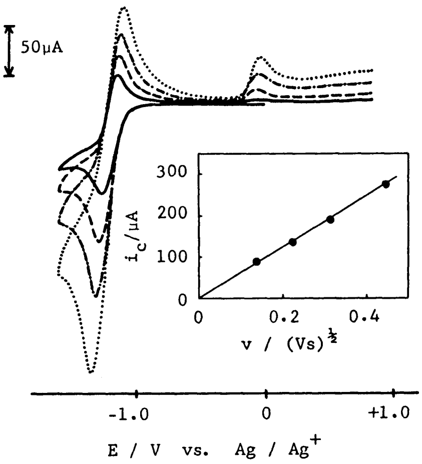


Fig. 3. Cyclic voltammograms of O_2 in the presence of 3 mM **1** at different sweep rates. ——: 0.02 V s^{-1}, ----: 0.05 V s^{-1}, —·—: 0.1 V s^{-1}, ······: 0.2 V s^{-1}. Inset. Sweep rate dependence of the cathodic peak current for the reduction of O_2 under 3 mM **1**.

Cyclic Voltammetry of Oxygen in the Presence of Active Methylene Compounds (1—4). As the first reduction potential of oxygen in a 0.2 M TEAP/DMF solution on glassy carbon electrode is −1.28 V, the dissolved oxygen is generally reduced more easily than active methylene compounds. Figure 2 indicates the cyclic voltammograms of saturated oxygen in the absence and presence of **1**. In the absence of **1**, the ratio of the anodic peak current (i_a^o) to the cathodic peak current (i_c^o) is almost 1.0; that is, the superoxide ion formed in this system is stable. In the presence of 2 mM **1**, the reductive peak current of oxygen at −1.28 V increased and the reoxidation peak current of the superoxide ion at −1.16 V decreased, in comparison with those in the absence of **1**. These results indicate that some of the superoxide ion are consumed by the reaction of **1**. The cathodic peak current of oxygen is linear to the square root of scan speed in the presence of **1** (Inset in Fig. 3). This means that the electrode reaction of oxygen is apparently diffusion-controlled, even if **1** is present in the system. The oxygen reduction behavior in the presence of other active methylene compounds **2**, **3**, and **4** gave similar to those of **1**. But the cyclic voltammograms of oxygen reduction in the case of **3** and **4** gave prepeaks. The prepeaks in the case of **3** is shown in Fig. 4.

The cyclic voltammetry of oxygen in the differrent concentrations of **1** is demonstrated in Fig. 5. Increasing the concentration of **1** resulted in a corresponding increase in the reduction peak current of oxygen. This increase of catalytic current did not continue

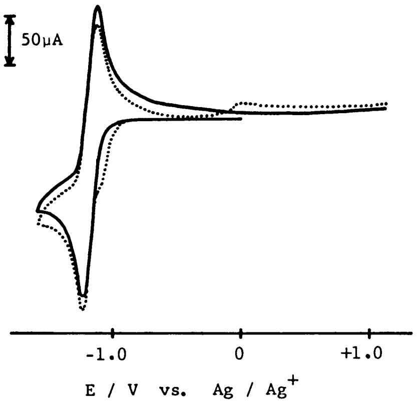


Fig. 4. Cyclic voltammograms of O_2 in the absence (——) and presence (······) of 2 mM **3**.
Sweep rate: 0.1 V s^{-1}.

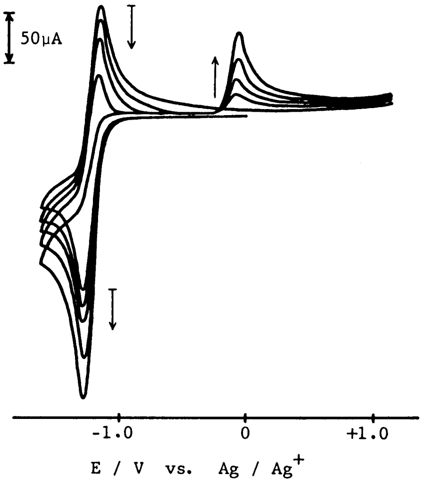


Fig. 5. Cyclic voltammograms of O_2 in the presence of different concentrations (0, 2, 4, 8, and 16 mM) of **1**.
Sweep rate: 0.1 V s^{-1}.

infinitely but reached a saturation at 18 mM **1**. The maximum value of the ratio, i_c/i_c^o, is ca. 1.65, where i_c and i_c^o are the reduction peak currents of oxygen in the presence and absence of **1**, respectively. These behavior is shown in Fig. 6. Increasing the concentration of **1** also resulted in a corresponding decrease in the reoxidation peak current of the superoxide ion. The peak current ratios, i_a/i_a^o are getting smaller with increasing concentrations of **1**, where i_a and i_a^o are the reoxidation peak currents of the superoxide ion in the presence and absence of **1**, respectively. These results also support that the electrogenerated superoxide ion is consumed by subsequent chemical reactions during cyclic voltammetry. The new anodic wave at −0.08 V (Fig. 5) is considered to be the oxidation peak characteristics of carbanion ($\bar{C}H(CO_2Et)_2$) at glassy carbon electrode, overlapped with the reoxidation wave of hydroperoxide ion (HO_2^-) formed by the following elementary reactions.

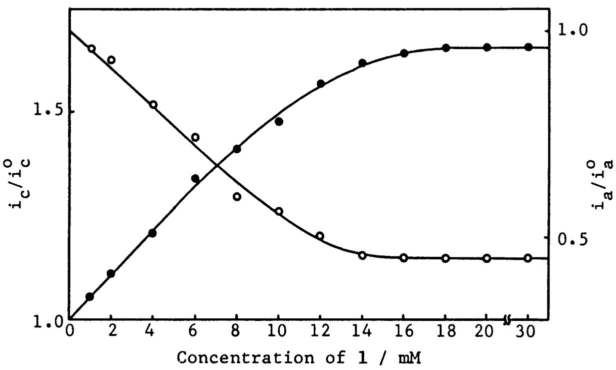
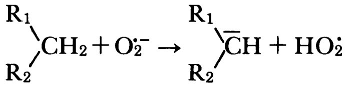


Fig. 6. Dependences of the peak current ratio for the concentration of **1**.
Sweep rate: 0.1 V s^{-1}, ●: i_c/i_c^o, O: i_a/i_a^o.

$$O_2 + e^- \rightarrow O_2^{\cdot -} \qquad (1)$$



$$R_1R_2CH_2 + O_2^{\cdot -} \rightarrow R_1R_2\bar{C}H + HO_2^{\cdot} \qquad (2)$$

$$HO_2^{\cdot} + e^- \rightarrow HO_2^- \qquad (3)$$

R_1, R_2: electron-withdrawing group (EWG)

The new anodic waves agreed with the oxidation peaks observed in the cyclic voltammogram of **1** by the addition of sodium ethoxide and in the cyclic voltammogram of H_2O_2 by the addition of tetraethylammonium hydroxide, respectively.

This oxidation peak current increased with the increasing concentrations of **1**. The increase did not continue infinitely, but reached a saturation in the presence of **1** of more than 18 mM. In the acetylacetone system, three new anodic peaks beside the oxidation peak of the superoxide ion formed appeared as shown in Fig. 7. The first anodic peak at −0.05 V and the second anodic peak at +0.10 V were assigned

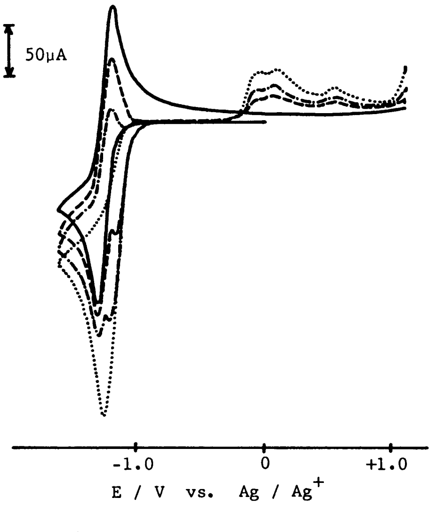


Fig. 7. Cyclic voltammograms of O_2 in the presence of different concentrations of **4**.
Sweep rate: 0.1 V s^{-1}, ——: 0 mM, ----: 4 mM, —·—: 8 mM, ······: 16 mM.

Table 2. Observed Peak Potentials in the CV of O_2 under **1**—**4**

	Reduction peak potential/V		Reoxidation peak potential/V			
	Prepeak	Oxygen	Superoxide ion	HO_2^-	Carbanion	Unknown
1	—	−1.28	−1.16	−0.08	−0.08	—
2	—	−1.28	−1.16	−0.06	−0.06	—
3	−1.20	−1.28	−1.17	−0.07	+0.00	+0.86
4	−1.18	−1.28	−1.16	−0.05	+0.10	+0.57

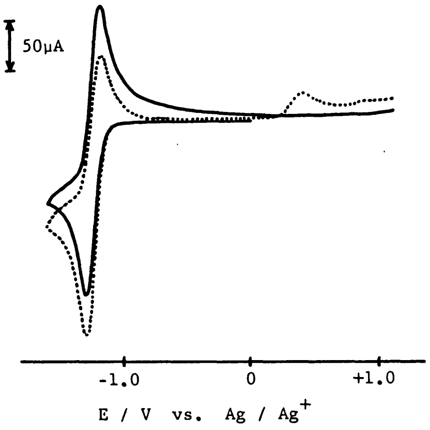


Fig. 8. Cyclic voltammograms of O_2 in the absence (——) and presence (······) of 2 mM **a**. Sweep rate: 0.1 V s^{-1}.

to the oxidation peaks of HO_2^- and $\bar{C}H(COCH_3)_2$, respectively. The second peak was confirmed to appear by the addition of sodium ethoxide. The third anodic peak was not reasonably assigned. The cyclic voltammograms of oxygen in the presence of **2** were very similar to those of **1** and those of **3** were similar to those of **4**. These results are summarized in Table 2.

By comparing the ratio of anodic peak current to cathodic peak current for the oxygen redox system in the presence of 8 mM active methylene compounds, the superoxide ion is found to react with active methylene compounds in the order of **4**(pK_a=9.0)>**3** (10.2)>**2**=**1**(13.5). This order is the same as that of acidity (pK_a) of active methylene compounds as carbon acids.

Cyclic Voltammetry of Oxygen in the Presence of Dibromoalkanes (a—g). As a typical result, the cyclic voltammetry of oygen in the presence of **a** is shown in Fig. 8. This cyclic voltammogram is very similar to that in the presence of **1**. In the presence of 2 mM **2**, the first reduction peak current of oxygen at −1.30 V increased, and the reoxidation peak current of the superoxide ion at −1.18 V decreased, in comparison with those of the saturated oxygen alone. These results indicate a progress of the reaction of superoxide ion with **a**. The cyclic voltammetry of oxygen in the presence of other dibromoalkanes (**b**—**g**) gave similar results to that of **a**.†

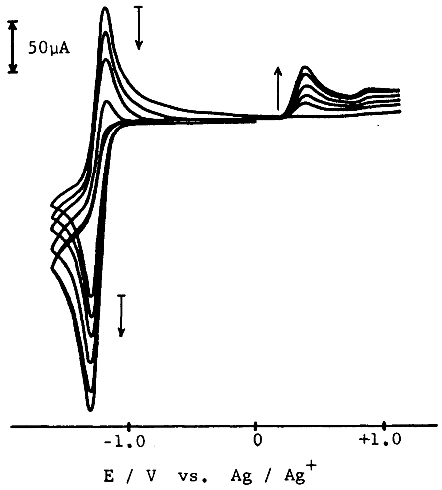


Fig. 9. Cyclic voltammograms of O_2 in the presence of different concentrations (0, 1, 2, 4, 8, and 16 mM) of **a**. Sweep rate: 0.1 V s^{-1}.

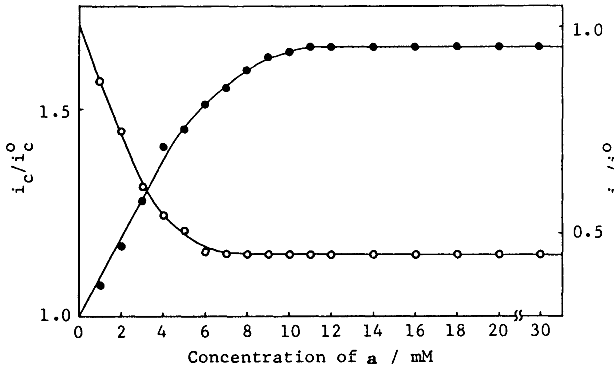


Fig. 10. Dependences of the peak current ratio for the concentration of **a**. Sweep rate: 0.1 V s^{-1}, ●: i_c/i_c^o, ○: i_a/i_a^o.

When dichloroalkanes were used in place of dibromoalkanes, no change of cyclic voltammogram in the absence and presence of dichloroalkanes was observed. This means that the superoxide ion is hard to react with dichloroalkanes. On the other hand, when diiodoalkanes were used in place of dibromoalkanes, the superoxide ion reacted with diiodoalkanes to reach a saturation at lower concentrations than dibromoalkanes.

The cyclic voltammetry of oxygen was also carried out in the different concentrations of dibromoalkanes. A typical result containing **a** is shown in Fig. 9.

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† The electrode reaction of oxygen is also apparently diffusion-controlled in the presence of **a**—**g**.

Table 3. Observed Peak Potentials in the CV of O_2 under **a**—**g**

	Reduction peak potential/V		Reoxidation peak potential/V		
	Prepeak	Oxygen	Superoxide ion	Bromide ion	Unknown
a	—	−1.30	−1.18	+0.38	+0.86
b	—	−1.30	−1.18	+0.33	+0.86
c	—	−1.29	−1.18	+0.33	+0.83
d	—	−1.29	−1.18	+0.35	+0.85
e	—	−1.29	−1.18	+0.40	+0.90
f	—	−1.30	−1.19	+0.32	+0.82
g	—	−1.30	−1.19	+0.32	+0.82

Increasing the concentration of **a** resulted in a corresponding increase in the reduction peak current and reached a saturation in the presence of 11 mM **a**. The maximum value of the ratio, i_c/i_c°, is ca. 1.65 and the same as in the presence of active methylene compounds. This behavior is demonstrated in Fig. 10. Two new anodic peaks at +0.38 V and +0.86 V observed in the presence of **a** can be ascribed to the oxidation of bromide ion which was produced by the nucleophilic substitution of the superoxide ion

$$\mathrm{Br(CH_2)_nBr + O_2^{\cdot-} \rightarrow Br(CH_2)_nOO\cdot + Br^-} \qquad (4)$$

with the dibromoalkane (Fig. 8). These oxidation peak currents also increased with the increasing concentrations of **a** and reached a saturation at the concentration of 11 mM. The cyclic voltammograms of oxygen in the presence of other dibromoalkanes (**b**—**g**) gave similar behavior to that of **a** and are summarized in terms of the potentials in Table 3.

Table 4. Reaction of Electrogenerated $O_2^{\cdot-}$ with Substrates

Substrate	Rate constant $k^{a)}$/$M^{-1}s^{-1}$
Diethyl malonate (**1**)	1×10^2
Dimethyl malonate (**2**)	1×10^2
Ethyl acetoacetate (**3**)	1×10^2
Acetylacetone (**4**)	1×10^2
1,2-Dibromoethane (**a**)	6×10^2
1,3-Dibromopropane (**b**)	6×10^2
1,4-Dibromobutane (**c**)	5×10^2
1,5-Dibromopentane (**d**)	6×10^2
1,6-Dibromohexane (**e**)	6×10^2
1,3-Dibromobutane (**f**)	6×10^2
1,4-Dibromopentane (**g**)	5×10^2

a) Determined by digital simulation based on the following mechanisms.

(1) $\mathrm{O_2 + e^- \longrightarrow O_2^{\cdot-}}$

$\mathrm{O_2^{\cdot-} + RH_2 \longrightarrow RH^- + HO_2^{\cdot}}$

$\mathrm{O_2^{\cdot} + e^- \longrightarrow HO_2^-}$

$\mathrm{R = (EWG)_2C}$

(2) $\mathrm{O_2 + e^- \longrightarrow O_2^{\cdot-}}$

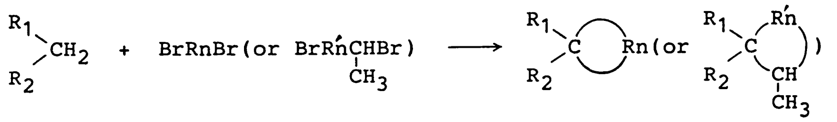
$\mathrm{O_2^{\cdot-} + RBr \longrightarrow ROO^{\cdot} + Br^-}$

$\mathrm{ROO^{\cdot} + e^- \longrightarrow ROO^-}$

$\mathrm{R = Br(CH_2)_n}$

Determination of Simple Rate Constants. In order to clarify each reaction rate of the electrogenerated superoxide ion with a variety of substrates, rate constants have been estimated based on a simple ECE reaction mechanism and the values determined by use of a digital simulation method are listed in Table 4. This is the method which simulates the ratio of enhancement of the cathodic peak current of oxygen reduction in the presence of substrate to that in the absence of substrate. The results indicate that the superoxide ion is more reactive with dibromoalkanes than with active methylene compounds. The rate constants for **3** and **4** could not be obtained accurately in the present simulation method, since the cyclic voltammograms of oxygen showed the prepeaks which might be a very rapid reaction between $O_2^{\cdot-}$ and **3** or **4**.

Controlled Potential Macro-Electrolysis. The controlled potential macro-electrolyses of oxygen in the presence of two kinds of substrates, active methylene compounds (**1**—**4**) and dibromoalkanes (**a**—**d**, **f**, and **g**) were carried out at −1.5 V in a 0.2 M TEAP/DMF solution. At −1.5 V, only oxygen was reduced to superoxide ion by one-electron transfer, while both



1: $R_1=R_2=CO_2Et$	**a**: $Rn=(CH_2)_2$	**5a**—**d**	**5f**, **g**
2: $R_1=R_2=CO_2Mt$	**b**: $Rn=(CH_2)_3$	**6a**—**d**	**6f**, **g**
3: $R_1=COCH_3$, $R_2=CO_2Et$	**c**: $Rn=(CH_2)_4$	**7a**—**d**	**7f**, **g**
4: $R_1=R_2=COCH_3$	**d**: $Rn=(CH_2)_5$	**8a**—**d**	**8f**, **g**
	e: $Rn=(CH_2)_6$		
	f: $R'n=(CH_2)_2$		
	g: $R'n=(CH_3)_3$		

Scheme 2.

the substrates, active methylene compounds and dibromoalkanes, were not reduced.

The main products were aliphatic cyclic or annulated compounds of one carbon extension comparing to the starting dibromoalkanes (Scheme 2).

Diethyl cycloalkanedicarboxylates (**5a—d**, **f**, and **g**) were produced from diethyl malonate and dibromoalkanes in the presence of electrogenerated superoxide ion, dimethyl cycloalkanedicarboxylates (**6a—d**, **f**, and **g**) from dimethyl malonate and dibromoalkanes, ethyl 1-acetylcycloalkanecarboxylates (**7a—d**, **f**, and **g**) from ethyl acetoacetate and dibromoalkanes, and 1,1-diacetylcycloalkanes (**8a—d**, **f**, and **g**) from acetylacetone and dibromoalkanes, respectively.

The electrolysis results are summarized in Table 5. Numbers in parentheses show the yields of the corresponding products by the ordinary chemical preparative method using sodium ethoxide as a base. The total amount of charge passed was ca. 482.5 C (2 F mol^{-1}). The yields by the electrochemical method and the ordinary chemical method are based on the consumed amount of active methylene compounds. The highest yield of the annulated compounds by the electrochemical method was 90% of **6c**. The yields of **5**, **6**, and **8** by the electrochemical method were higher than those by the chemical method except the case of **5f**. However, the yields of **7** were of the inverse tendency. The yields of the annulated products depended markedly on the methylene length of α,ω-dibromoalkanes, and the yields of stable ring size such as five or six membered ring were generally high. The reason can be explained by the degree of strain, when the ring closure occurs.

In the case of **1** or **2** as active methylene compound, the yields of the annulated products by the electrochemical method decreased in the order of $C_5>C_6>C_4>C_3$, similarly to those observed in the ordinary chemical reaction. In the case of **3**, a somewhat different tendency was observed. For instance, the yields by the electrochemical method decreased in the order of $C_6>C_5>C_4\approx C_3$, whereas the yields by the chemical method was in the order of $C_5>C_4\approx C_6>C_3$.

Table 5. Yields of Annulated Products by Preparative Electrochemical Method

Substrate No.	Product No.	Dibromoalkane a	b	c	d	f	g
1	**5**	49%	51%	87%	82%	20%	83%
		(28%)	(43%)	(66%)	(50%)	(48%)	(58%)[a]
2	**6**	52%	55%	90%	81%	17%	89%
		(4%)	(19%)	(20%)	(21%)	(14%)	(36%)
3	**7**	28%	30%	35%	56%	27%	29%
		(20%)	(58%)	(58%)	(67%)	(45%)	(61%)
4	**8**	19%	68%	72%	58%	36%	37%
		(3%)	(16%)	(23%)	(25%)	(21%)	(22%)

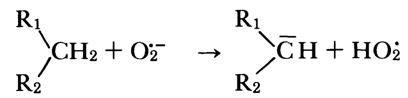
a) Numbers in parentheses show the yields of the corresponding products by the chemical preparative method in which 0.01 mol each of active methylene compound and dibromoalkane was reacted with 0.02 g·atom sodium ethoxide in ethanol at 80 °C.

The use of branched dibromoalkanes such as 1,3-dibromobutane (**f**) and 1,4-dibromopentane (**g**) decreased the yields of the annulated products in comparison to those of the same membered ring products formed from α,ω-dibromoalkanes; the yields of **5—8f**, and **7g**, **8g** are lower than those of **5—8c** and **7d**, **8d**, respectively (excluding the cases of **5f**=**5d** and **6f**>**6d**). This trend may be caused by steric hindrance of methyl branch at the carbon substituted.

From the above mentioned results, the following electrochemical reaction mechanism for the system of malonic acid ester and α,ω-dibromoalkane can be presented:

Mechanism 1: Superoxide ion as an EGB

$$O_2 + e^- \rightarrow O_2^{\cdot-} \quad (1)$$



$$\underset{R_2}{\overset{R_1}{>}}CH_2 + O_2^{\cdot-} \rightarrow \underset{R_2}{\overset{R_1}{>}}\bar{C}H + HO_2^{\cdot} \quad (2)$$

$$HO_2^{\cdot} + e^-(O_2^{\cdot-}) \rightarrow HO_2^- \quad (3)$$

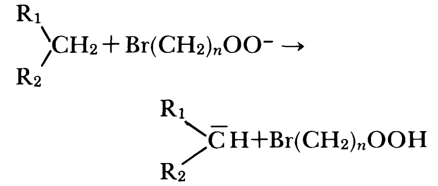
Mechanism 2: Superoxide ion as a nucleophile

$$O_2 + e^- \rightarrow O_2^{\cdot-} \quad (1)$$

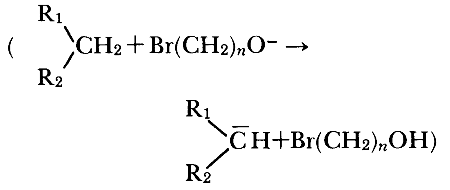
$$Br(CH_2)_nBr + O_2^{\cdot-} \rightarrow Br(CH_2)_nOO^{\cdot} + Br^- \quad (4)$$

$$Br(CH_2)_nOO^{\cdot} + e^-(O_2^{\cdot-}) \rightarrow Br(CH_2)_nOO^- \quad (5)$$

$$\rightarrow Br(CH_2)_nO^- \quad (6)$$

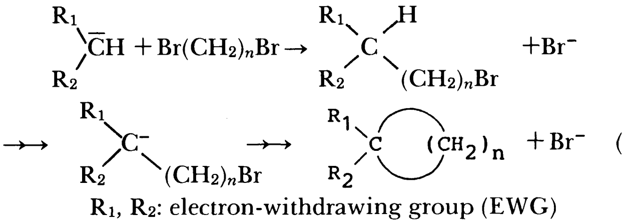


$$\underset{R_2}{\overset{R_1}{>}}CH_2 + Br(CH_2)_nOO^- \rightarrow \underset{R_2}{\overset{R_1}{>}}\bar{C}H + Br(CH_2)_nOOH \quad (7)$$



$$\left(\underset{R_2}{\overset{R_1}{>}}CH_2 + Br(CH_2)_nO^- \rightarrow \underset{R_2}{\overset{R_1}{>}}\bar{C}H + Br(CH_2)_nOH\right) \quad (8)$$

……



(9)

R$_1$, R$_2$: electron-withdrawing group (EWG)

In mechanism 1, superoxide ion, as an electrogenerated base (EGB), deprotonates an active methylene compound (Eq. 2), and the resulting carbanion reacts with α,ω-dibromoalkane to yield the aliphatic annulated compound (Eq. 9). In mechanism 2, superoxide ion, as a nucleophile, reacts with α,ω-dibromoalkane, and the produced bromoalkylperoxy radical (Eq. 4) is further reduced by superoxide ion or by an electron from the electrode to form bromoalkylperoxide ion

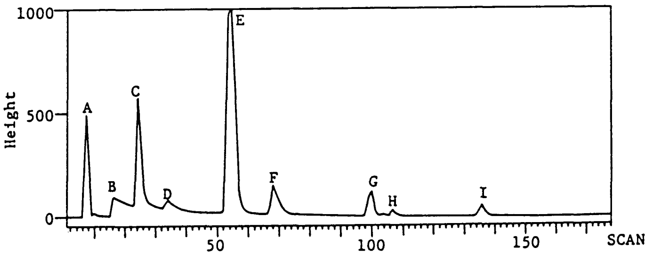
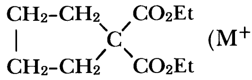
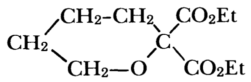


Fig. 11. Typical gas chromatogram of the reaction of $O_2^{\cdot -}$ with **1** and **c**.
A: acetone, B: DMF, C: $CH_2(CO_2Et)_2$,
D: $Br(CH_2)_4Br$,

E: 

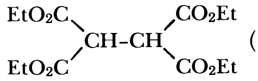
$$\begin{array}{l} CH_2\text{-}CH_2\quad CO_2Et \\ |\qquad\qquad C \\ CH_2\text{-}CH_2\quad CO_2Et \end{array}$$

$(M^+=215)$,

F: 

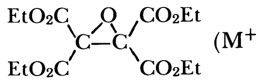
$$\begin{array}{l} \quad CH_2\text{-}CH_2\quad CO_2Et \\ CH_2\qquad\qquad C \\ \quad CH_2\text{—}O\quad CO_2Et \end{array}$$

$(M^+=231)$,

G: 

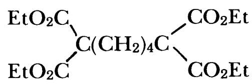
$$\begin{array}{l} EtO_2C\qquad\qquad CO_2Et \\ \qquad CH\text{-}CH \\ EtO_2C\qquad\qquad CO_2Et \end{array}$$

$(M^+=319)$,

H: 

$$\begin{array}{l} EtO_2C\quad O\quad CO_2Et \\ \qquad C\text{—}C \\ EtO_2C\qquad CO_2Et \end{array}$$

$(M^+=333)$,

I: 

$$\begin{array}{l} EtO_2C\qquad\qquad CO_2Et \\ \qquad C(CH_2)_4C \\ EtO_2C\qquad\qquad CO_2Et \end{array}$$

$(M^+=375)$.

(Eq. 5) or bromoalkyloxide ion (Eq. 6). The resulting anions deprotonate, as a base, the active methylene compound (Eqs. 7 and 8), and the produced carbanion reacts with α,ω-dibromoalkane to yield the aliphatic annulated compound as mechanism 1 (Eq. 9). The similar reaction mechanism can be presented in the other cases of branched dibromoalkanes.

In addition to the annulated compounds, cyclic ethers such as tetrahydrofuran and diols such as 1,4-butanediol from **c** were also detected as minor products by the careful gas chromatographic analysis at room temperature, and identified by comparing their retention times with those of authentic samples. Other by-products, mainly some dimers, were detected and assigned using GC-MS spectroscopy. The gas chromatogram in the case of the reaction of $O_2^{\cdot -}$ with **1** and **c** is demonstrated in Fig. 11, and each peak was assigned to the compound shown in the figure, respectively. Most of these by-products were not detected in the products by the ordinary chemical method.

These results indicate that the reaction mechanism for the present electrochemical reaction might be partly different from that for the ordinary chemical reaction. The main difference is that electrogenerated superoxide ion forms intermediates shown in Eqs. 4—6, whereas sodium ethoxide does not form such intermediates. Therefore, the carbanion formation via Eqs. 7 and 8 cannot proceed by the ordinary chemical method.

Conclusion

Perkin–Markovnikov type reaction initiated with electrogenerated superoxide ion was investigated electrochemically using cyclic voltammetry and controlled potential macro-electrolysis. By electrolyses, superoxide ion acted as a base and a nucleophile, and reacted with both the substrates, active methylene compounds and dibromoalkanes, to yield the end products, aliphatic cyclic compounds. This electrochemical method can be applied to synthesize one carbon-extended cyclic compounds from dibromoalkanes.

Besides these compounds as the main products, many by-products, such as dimers and cyclic ethers were detected using GC-MS spectroscopy. The formation reaction of the cyclic ethers is a novel reaction which has never been seen in the usual base-catalyzed reactions. All of these results are based on the dual nature of electrogenerated superoxide ion; i.e., basicity and nucleophilicity, which vary with substrates.

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