OXIDATION OF METHYLPYRIDINES AND METHYLPYRIDINE-N-OXIDES WITH ELECTRO-GENERATED SUPEROXIDE ION.

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The oxidation of methylpyridines and methylpyridine-N-oxides with electro-generated superoxide ion in DMF was studied by cyclic voltammetry and controlled potential macro-electrolysis. The electrochemical reduction of oxygen in the presence of these compounds yielded the corresponding carboxylic acids. The reactivity of the methyl groups towards the oxidation varied according to the location of such groups on the heterocyclic ring and was in each case greater for the methylpyridine-N-oxide than for the corresponding methylpyridine.

Recently the superoxide ion, $O_2^{\cdot-}$, has attracted a great deal of attention from organic and biological chemists, because it is novel activating reagent for organic synthesis and is one of the most important activated forms of molecular oxygen in biological systems[1]. Superoxide ion is produced by the electrochemical reduction of oxygen dissolved in non-aqueous solvents, such as pyridine, acetonitrile, and dimethylformamide (DMF), at -0.9 V vs. a saturated calomel electrode (SCE)[2,3] as shown in Eq. (1):

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

Alkali metal superoxides, such as potassium and sodium superoxides, are well known, but their insolubility in the usual organic solvents makes them of little preparative use[4]. The electrochemical method is experimentally more convenient because the continuous generation of superoxide ion is possible on the electrode and the solubility of the superoxide ion in the presence of tetraalkylammonium cations of the supporting electrolyte is sufficiently high[5].

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We have previously reported that the reaction of nitrotoluene and nitroethylbenzene with electro-generated superoxide ion yielded the corresponding nitrobenzoic acid from the former and nitroacetophenone plus nitrophenethyl alcohol from the latter[6]. In order to investigate the nature of such reaction with the alkyl groups of heterocyclic compouds, we have studied, and describe here, the reaction of methyl groups of methylpyridines and methylpyridine-N-oxides with the superoxide ion , using macro-electrolysis and cyclic voltammetry in DMF solution.

Cyclic voltammetry was carried out in DMF solution containing tetraethylammonium perchlorate (TEAP) as the supporting electrolyte on a hanging mercury drop electrode (HMDE). Potentials are referred to an SCE. For controlled potential macro-electrolysis, an H-type cell was employed in which cathodic and anodic chambers were separated by two porous glass disks, and a reference electrode with a Luggin capillary was put near the cathode. A mercury pool with a surface area of 16 cm^2 was used as the cathode. An electrolyte solution, 60 cm^3 containing 0.05 M substrate and 0.1 M TEAP, was placed in the cathodic chamber and 40 cm^3 of the electrolyte solution in the anodic chamber, and oxygen was bubbled through the catholyte. The cathode potential was controlled with a Yanagimoto VE-8 controlled potential electrolyzer. DMF was dried over anhydrous $CuSO_4$ for 24 h, distilled under reduced pressure, and further purified by passage through a column of activated alumina. TEAP was synthesized and purified in the usual manner[7].

A cyclic voltammogram of oxygen in DMF solution is shown in Fig. 1. The first reversible reduction wave at -0.9 V vs. SCE corresponds to the one-electron reduction of oxygen to the superoxide ion. The second irreversible reduction wave

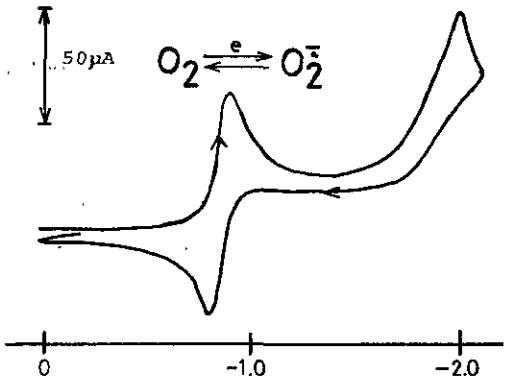

Fig. 1. Cyclic voltammograms of oxygen. elctrolyte: 0.1 M TEAP/ DMF, electrode: HMDE, sweep rate: 0.1 Vs^{-1}.

at -1.8 V vs. SCE corresponds to the further one-electron reduction of the superoxide ion to the peroxide ion, O_2^{2-}, followed by protonation.

The reduction peak potentials of methylpyridines and methylpyridine-N-oxides, together with that for oxygen, in their cyclic voltammograms are shown in Table 1. The reduction waves for methylpyridines did not appear in the potential region from 0 to -2.5 V vs. SCE. The irreversible reduction waves for methylpyridine-N-oxides appeared at ca. -2.3 V vs. SCE. Cyclic voltammograms of 4-methylpyridine-N-oxide in the presence and in the absence of oxygen are shown in Fig. 2. In the

Table 1. Reduction peak potentials of methylpyridines and methylpyridine-N-oxides

Compound	E_p^1	E_p^2
2-methylpyridine	< -2.5	
3-methylpyridine	< -2.5	
4-methylpyridine	< -2.5	
2-methylpyridine-N-oxide	-2.31	
3-methylpyridine-N-oxide	-2.35	
4-methylpyridine-N-oxide	-2.34	
cf. oxygen molecule	-0.9	-1.80

E/ V vs. SCE, solvent: DMF, supporting electrolyte: TEAP, electrode: HMDE.

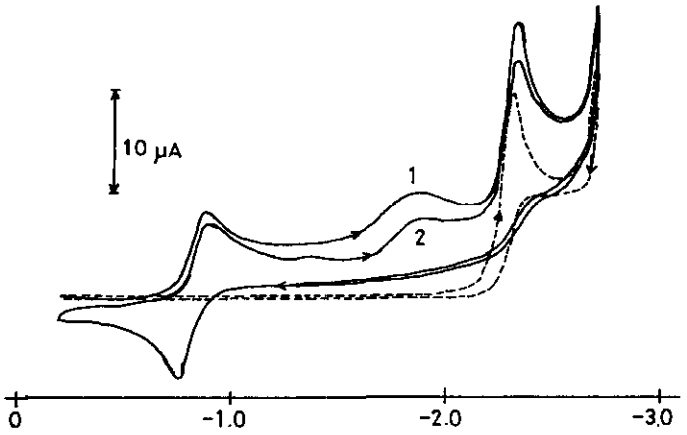

Fig. 2. Cyclic voltammograms of 4-methylpyridine-N-oxide in the presence (——) and in the absence (---) of oxygen. electrolyte: 0.1 M TEAP/ DMF, electrode: HMDE, sweep rate: 0.1 Vs^{-1}, 1: the first sweep, 2: the second sweep.

presence of oxygen, the first and second reduction waves are the corresponding oxygen reduction waves mentioned above, and the third wave is the reduction wave for methylpyridine-N-oxide. In this case no other reduction wave appeared.

The controlled potential macro-electrolyses of oxygen in the presence of methylpyridines and methylpyridine-N-oxides were carried out at -0.9 V vs. SCE in DMF solution. The electrolysis time was ca. 16 h and the total amount of charge passed was ca. 1700-1800 C. The yields of products were determined using a JASCO FLC-150 high pressure liquid chromatography system with a JASCO UVIDEC-1 recording spectrophotometer [column: JASCO PACK SS-05-500, eluent: chloroform:methanol=1:1]. Pyridinecarboxaldehydes or pyridinecarboxaldehyde-N-oxides, assumed to be intermediates in the oxidations, were not detected by the present analysis. These intermediates are therefore considered to be instantly oxidized to the final products, the corresponding carboxylic acids. The carboxylic acids, the main products of the oxidations, were separated and identified by the following procedure. The catholyte was poured into 10 % aqueous $NaHCO_3$ solution and the starting material was removed by extraction with CH_2Cl_2. The aqueous layer was neutralized with 5 % aqueous HCl and evaporated to dryness in vacuo. Since the resulting solid consisted of products, supporting electrolyte, and NaCl, chromatographic separation was carried out on a column of silica gel using chloroform-methanol as eluent. This chromatographic separation was repeated several times until purification by recrystallization from methanol became possible. The products thus purified were identified as the expected carboxylic acids by comparing thier infrared spectra with those of authentic samples purchased commercially (Wako Pure Chemical Industries and Aldrich) or prepared separately[8,9]. As described later, the peak potentials of the cyclic voltammograms of these products were also found to agree with those of the authentic carboxylic acids.

The results of the electrolyses are collected in Table 2. 4-Methylpyridine reacted with electro-generated superoxide ion to yield 4-pyridinecarboxylic acid. 2- and 4-methylpyridine-N-oxides reacted with superoxide ion to yield 2- and 4-pyridinecarboxylic acid N-oxides respectively. From 2-methylpyridine and 3-methylpyridine-N-oxide only trace amounts of the corresponding carboxylic acids were obtained. No carboxylic acid was obtained from 3-methylpyridine. In the reactions of the methyl groups of methylpyridines and methylpyridine-N-oxides with amyl nitrite or with methyl iodide, the methyl group of a methylpyridine is much less reactive than that of the corresponding N-oxide , and, the reactivity of methyl

Table 2. Controlled potential macro-electrolyses of oxygen in the presence of methylpyridines and methylpyridine-N-oxides.

Starting material	product	yield/ %
2-methylpyridine	2-pyridinecarboxylic acid	trace
3-methylpyridine	——	——
4-methylpyridine	4-pyridinecarboxylic acid	11
2-methylpyridine-N-oxide	2-pyridinecarboxylic acid N-oxide	33
3-methylpyridine-N-oxide	3-pyridinecarboxylic acid N-oxide	trace
4-methylpyridine-N-oxide	4-pyridinecarboxylic acid N-oxide	28

groups on the pyridine ring increases in the order 3-, 2-, and 4-substitution[10-12]. These results agree well with the present results of the reactivity of electro-generated superoxide ion with methylpyridines and methylpyridine-N-oxides.

After macro-electrolysis of oxygen in the presence of 4-methylpyridine, cyclic voltammetry of the catholyte was carried out. The results are shown in Fig. 3. A and B are the cyclic voltammograms of the catholyte after electrolysis; A was measured under air-saturation and B was measured after deaeration with nitrogen. C is the cyclic voltammogram of the catholyte before electrolysis under nitrogen. On curve C, no reduction wave appears in the potential region from 0 to -2.5 V vs. SCE, while on curve B new reduction waves appear at -1.8 V and -2.5 V vs. SCE.

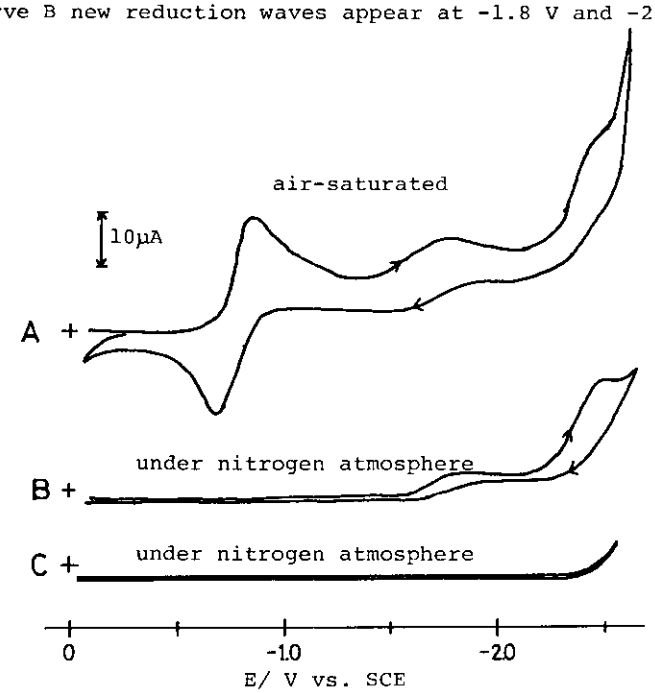

Fig. 3. Cyclic voltammograms of the catholyte in the presence of 4-methylpyridine. electrode: HMDE, elctrolyte: 0.1 M TEAP/ DMF.

The reduction wave at -2.5 V vs. SCE corresponded to the reduction of 4-pyridinecarboxylic acid, but the compound which gave the reduction wave at -1.8 V vs. SCE is unknown at present. These results indicated that 4-pyridinecarboxylic acid was produced by the reaction of electro-generated superoxide ion with 4-methylpyridine.

Cyclic voltammograms of the catholyte after macro-electrolysis of oxygen in the presence of 4-methylpyridine-N-oxide are shown in Fig. 4. On curve B, the second reduction wave at ca. -2.3 V vs. SCE is that of the starting 4-methylpyridine-N-oxide, while the first wave at ca. -2.1 V vs. SCE is absent in the cyclic voltammogram of 4-methylpyridine-N-oxide (Fig. 2) and only appeared after macro-electrolysis. This new reduction peak potential agreed with that of 4-pyridinecarboxylic acid N-oxide prepared separately[8]. In the cyclic voltammogram of 4-methylpyridine-N-oxide in the presence of oxygen (solid line in Fig. 2), no other reduction wave appeared except those for oxygen and 4-methylpyridine-N-oxide. These results indicate that 4-pyridinecarboxylic acid N-oxide was not formed during

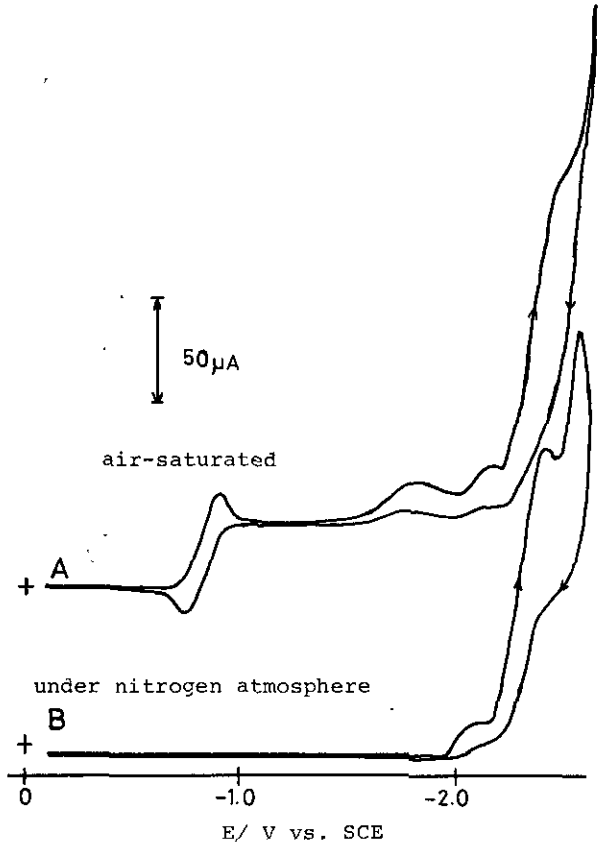

Fig. 4. Cyclic voltammograms of the catholyte in the presence of 4- methylpyridine-N-oxide. electrolyte: 0.1 M TEAP/ DMF, electrode: HMDE.

cyclic voltammetry, and consequently the reaction rate of the superoxide ion with 4-methylpyridine-N-oxide was slow.

A reaction scheme for the oxidation of methylpyridines and methylpyridine-N-oxides with the electro-generated superoxide ion can be suggested as shown in Scheme 1. One of the hydrogen atoms of the methyl group of the methylpyridine or

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

$$R\text{-}CH_3 + O_2^{\cdot-} \longrightarrow R\text{-}CH_2^{\cdot} + HO_2^- \quad (2)$$

$$R\text{-}CH_2^{\cdot} + O_2 \longrightarrow R\text{-}CH_2OO\cdot \quad (3)$$

$$R\text{-}CH_2OO\cdot + O_2^{\cdot-} \longrightarrow R\text{-}CH_2OO^- + O_2 \quad (4)$$

$$R\text{-}CH_2OO^- \longrightarrow R\text{-}CHO + OH^- \quad (5)$$

$$R\text{-}CHO + O_2^{\cdot-} \text{ (or e from electrode)} \longrightarrow R\text{-}CO\cdot + HO_2^- \quad (6)$$

$$R\text{-}CO\cdot + HO_2^- \longrightarrow [R\text{-}COOOH]^{\cdot-} \quad (7)$$

$$[R\text{-}COOOH]^{\cdot-} \longrightarrow R\text{-}COO\cdot + OH^- \quad (8)$$

$$R\text{-}COO\cdot + O_2^{\cdot-} \text{ (or e from electrode)} \longrightarrow R\text{-}COO^- + O_2 \quad (9)$$

Scheme 1

methylpyridine-N-oxide is abstracted by the electro-generated superoxide ion in DMF solution (Eq. (2)). The resulting species reacts with oxygen (Eq. (3)) and is further reduced to the peroxy anion by superoxide ion or electron from eletrode (Eq. (4)). In a basic solvent such as DMF, the release of the hydroxyl anion from this peroxy ion, which yields aldehyde (Eq. (5)), occurs predominantly, rather than the proton abstraction from environments by the peroxy anion[13]. This aldehyde reacts instantly with superoxide ion to yield an acyl radical (Eq. (6)). This acyl radical reacts with hydrogen peroxide ion (Eq. (7)), and hydroxide anion is released from the resulting percarboxylic acid anion radical and yields the carboxyl radical (Eq. (8)). This carboxyl radical is finally reduced to carboxyl anion by the superoxide ion or electron from electrode (Eq. (9)).

ACKNOWLEDGEMENTS

We thank the Japan Society for Promotion of Science for the provision of funds during the period (Feb. - April 1976) when one of us (H.L.) was a Visiting Professor at Tohoku University. The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education (No. 47017).

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Received, 19th November, 1979