Polarography of Pyridine N-Oxide and its Alkyl Derivatives[*1]

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(Received April 23, 1962)

Several authors have reported on the polarographic behavior of such aliphatic and aromatic *N*-oxides as pyridine, nitrogen mustard and narcotin *N*-oxides, showing that these *N*-oxides give one or more reduction waves involving two electrons and are reduced to the corresponding amines[1-4]. Especially, Foffani and Fornasari have found that pyridine *N*-oxide in various buffer solutions gives one reduction wave whose height decreases rapidly at above pH≈6 and disappears in alkali[4]. The mechanism of such polarographic behavior, however, has not yet been studied in detail. In order to obtain further information about this mechanism, the present authors have attempted detailed polarographic investigations.

Experimental

A Yanagimoto pen-recording polarograph, model PB-4, a Beckman pH meter, model G, and a Hitachi recording spectrophotometer, model EPS-2, were used for the measurement of polarograms, pH values, and ultraviolet absorption spectra respectively. The characteristics of the dropping mercury electrode used were: $m=1.23$ mg./sec., $h=65$ cm. and $t=4.35$ sec. (open circuit). The ionic strength of the buffer solutions used, had been adjusted to 0.45 by adding sodium chloride; these buffer solutions were as follows: NaAc+HCl (pH=1.09~3.79), NaAc+HAc (pH=3.80~5.60), KH_2PO_4+NaOH (pH=6.20~7.40), and glycocol+NaCl+NaOH (pH =8.53~11.01). Polarograms were taken in the above buffer solutions after bubbling nitrogen gas for 10 min. to remove the dissolved oxygen in the solutions, saturated calomel electrode being used as the external reference electrode. In this case, the temperature was controlled within ±0.1°C by a thermostat, and the measurements were usually made at 25±0.1°C. Experiments were carried out three times on the same electrolytic solution. The values thus obtained were averaged.

Pyridine, 4-methylpyridine and 4-ethylpyridine *N*-oxides were prepared and purified by the standard method[5], and their melting points were determined to be 66, 184~185 and 108~109°C respectively. Infrared spectra and microanalytical data show good agreement with the data in the literature[6] and with the calculated values.

Results and Discussion

Polarograms of pyridine *N*-oxide at various pH values are illustrated in Fig. 1. The pH-dependence of the limiting current in pyridine and 4-methylpyridine *N*-oxides is also shown in Figs. 2 and 3. From Figs. 1, 2 and 3, it can be clearly seen that the reduction wave decreases rapidly with the increasing pH value in pH values above 5. Since the ultraviolet absorption spectra of each of the above *N*-oxides in a region of pH≈7 to 1 N sodium hydroxide coincide almost completely in both the maximum wavelength and the intensity, no change in the structure is expected in alkali. On the other hand, the acid dissociation constants (pK_a's) of pyridine and 4-methylpyridine *N*-oxides have previously been determined by the spectrophotometric method as 0.79 and 1.29 respectively[7,8]. Moreover, the experimental results of the temperature dependence and the mercury pressure dependence on the reduction wave in the acidic pH region and in the pH region in which the limiting current decreases rapidly are shown in Table I.

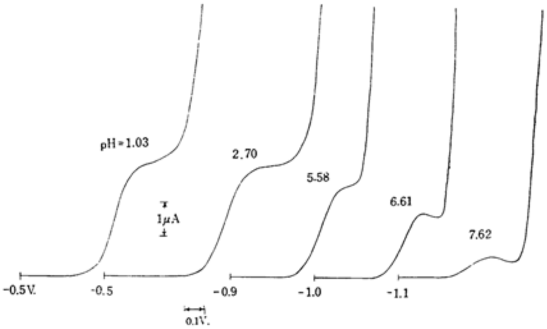


Fig. 1. Polarograms of pyridine *N*-oxide at various pH's.
Concn.: 5.28×10^{-4} mol./l., temp.: 25°C, ionic strength: 0.45

[*1] Polarographic Study of Aromatic *N*-Oxides I.

[1] E. Ochiai, *J. Pharm. Soc. Japan* (*Nippon Yakugaku Zasshi*), **69**, 1 (1949).

[2] I. Aiko, *Pharm. Bull.*, **1**, 335 (1953).

[3] Y. Asahi, This Bulletin, **34**, 1185 (1961).

[4] A. Foffani, and F. Fornasari, *Gazz. Chim. Ital.*, **83**, 1051, 1059 (1953).

[5] E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

[6] H. Shindo, *Chem. & Pharm. Bull.*, **7**, 791 (1959); **6**, 117 (1958); **4**, 460 (1956).

[7] a) T. Kubota, *J. Pharm. Soc. Japan* (*Nippon Yakugaku Zasshi*), **75**, 1546 (1955); b) T. Kubota, *J. Spectroscopical Soc. Japan*, **10**, 83 (1962).

[8] H. H. Jaffé and G. O. Doak, *J. Am. Chem. Soc.*, **77**, 4441 (1955).

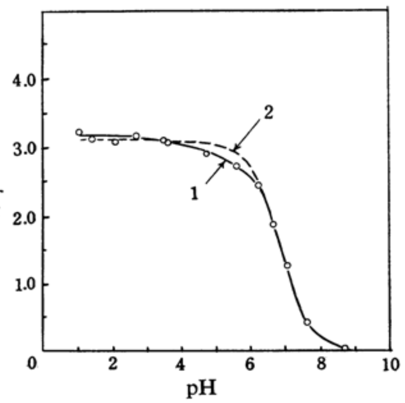


Fig. 2. The pH dependence of the limiting current of pyridine *N*-oxide.
Concn.: 5.28×10^{-4} mol./l., temp.: 25°C, ionic strength: 0.45. The relationship between pH and $E_{1/2}$ (in volt) fulfills the equation $-0.865[\text{pH}]-0.849$ in a region of pH=1.5~6.7.
1: Experimental curve
2: Calculated curve

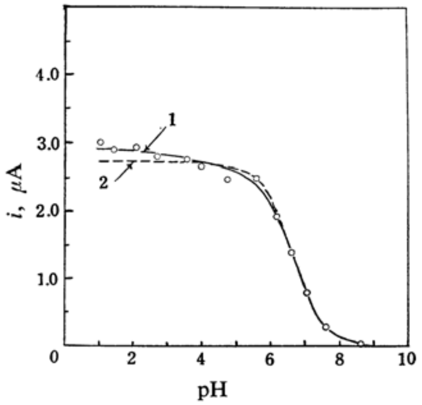
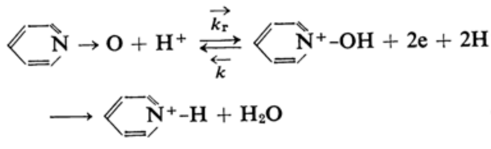


Fig. 3. The pH dependence of the limiting current of 4-methylpyridine *N*-oxide.
Concn.: 5.07×10^{-4} mol./l., temp.: 25°C, ionic strength: 0.45. The relationship between pH and $E_{1/2}$ fulfills the equation $E_{1/2}=-0.0948[\text{pH}]-0.883$ in a region of pH=1.5~6.7.
1: Experimental curve
2: Calculated curve

In the case of pH 7.0, the temperature coefficient of the reduction wave is much greater than that at pH 2.91. Moreover, the mercury pressure dependence at pH 7.0 did not show a good relationship between i and $\sqrt{h}$, where i and h denote the limiting current (μA) and the height of a mercury electrode in cm. (corrected with the reverse pressure of mercury height) respectively. In the case of pH 2.91, however, a linear relationship of i to $\sqrt{h}$ was obtained. In addition, the limiting current independent of $\sqrt{h}$ is zero or vevy small at pH 2.91 on the pyridine and 4-methylpyridine *N*-oxides, as may be seen in Table I.

From the viewpoint of the recent kinetic current theory⁹⁾, therefore, it may be reasonably considered on the basis of the above experimental results that the pH dependence of the limiting current is due to the kinetic current, which can be represented as Eqs. 1 and 2, which were derived by Matsuda and by Koutecky[10,11].



(1)

$$i=i_d\cdot[1/[1+1.128(\overrightarrow{k_r}\cdot t\cdot[\text{H}^+]^2/K_a)^{-1/2}]] \qquad (2)$$

Hence, i_d is the diffusion current corresponding to the total concentration of *N*-oxides. In our case, the i appearing in the region of high proton concentrations becomes equivalent to i_d, which may show the normal temperature and mercury pressure dependences, as was observed at pH 2.91 on the above *N*-oxides, because in this condition the term in the brackets on the right hand side of Eq. 2 is reduced to 1.

Using Eq. 2 and the K_a value above stated, we have determined the rate constant, $\overrightarrow{k_r}$, of the recombination process in Eq. 1, whereas for the drop time, t, the values measured under the same condition as the determination of limiting current were used, so as to satisfy the pH dependence of the limiting current; $\overrightarrow{k_r}=3.0\times10^{12}$ and $\overrightarrow{k_r}-3.7\times10^{11}$ (mol./l.)$^{-1}$(sec.)$^{-1}$ were obtained for pyridine *N*-oxides and 4-methylpyridine *N*-oxide respectively[*2].

The rate constants thus obtained are of the same order as the theoretical value obtained by Onsager[12] and as the experimental values of the other compounds determined by other workers[11]. The current-pH relationships calculated by using these k_r values are also shown in Figs. 2 and 3. A good agreement with the experiments is obtained on the whole. Some discrepancy, however, can be found in the acidic pH region. No quantitative explanation could be made for this, but it seems that the other miscellaneous effects on the *N*-oxide

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9) See the following reviews; M. Takagi, *Review of Polarography*, **9**, 53 (1961); M. Senda, ibid., **6**, 95 (1958); H. W. Nürnberg, *Angew. Chem.*, **72**, 433 (1960).

10) a) J. Koutecky, *Coll. Czecho. Chem. Communs.*, **18**, 183, 597 (1953); **19**, 857 (1954); b) H. Matsuda and Y. Ayabe, This Bulletin, **28**, 422 (1955).

11) R. Bridicka, *Z. Elektrochem.*, **64**, 16 (1960).

[*2] Applying Ilkovic's equation, $i_d=607\text{n.c.}D^{1/2}m^{2/3}t^{1/6}$, with i_d, m and t at pH=2.5~4.7 and D=7.7 or 8.68×10^{-6} cm²/sec., which figures are estimated from the molecular weight or from the equivalent conductance at an infinite dilution of such analogous organic ions as benzoic acid, n=2.1~2.4 is obtained.

12) L. Onsager, *J. Chem. Phys.*, **2**, 599 (1934).

TABLE I. THE TEMPERATURE AND THE PRESSURE DEPENDENCES FOR THE REDUCTION WAVE AT VARIOUS pH'S

Compound	Temperature coefficient (deg^{-1})[a]		Pressure dependence[b]	
Pyridine *N*-oxide	pH=2.91	pH=7.0	pH=2.91	pH=7.0
	1.05%	2.42%	$i=0.476\cdot\sqrt{h}$	c)
4-Methylpyridine *N*-oxide	pH=3.30	pH=6.61	pH=3.30	pH=6.61
	1.31%	2.06%	$i=0.304\sqrt{h}+0.375$	d)

a) Calculated at compound interest method.
b) h and i denote the height of a mercury electrode in cm. (corrected against the reverse pressure) and the limiting current (μA), respectively.
c) No good relationship between i and $\sqrt{h}$ exists.
d) No rigid relationship between i and $\sqrt{h}$ is obtained, but can be roughly expressed as $i=0.71+0.092\sqrt{h}$.

group, such as the hydration and the acid catalytic reactions, may contribute somewhat in the acidic pH region*3.

The current pH relationship of 4-ethylpyridine *N*-oxide also showed the same tendency as in Figs. 2 and 3. In this case, $\overrightarrow{k_r}=5.5\times10^{11}$ (mol./l.)$^{-1}$(sec.)$^{-1}$ was obtained by using Eq. 2, and p$K_a\fallingdotseq1.21$, which is estimated from the relationship between pK_a and Hammett's σ values[8].

Under the conditions used here, the reduction wave corresponding to the free *N*-oxide group could not be found; this point differs from that in such aliphatic compounds as narcotin *N*-oxide. As a result of the resonance effect between $\geqslant N\rightarrow O$ group and pyridine ring, as is well known, the aromatic *N*-oxide group shows a great resistance to the reductive reaction[5,7b].

Summary

The polarographic behavior of pyridine, 4-methylpyridine and 4-ethylpyridine *N*-oxides has been investigated. The reduction wave of these *N*-oxides decreases rapidly with the increasing pH value in pH values above 5 and disappears in alkali. It was clearly shown by the polarographic and spectroscopic investigations that the main reason for this phenomenon is the kinetic current. Quantitative treatment of the pH-dependence of the limiting current was also carried out.

The authors are grateful to Professor Shinzi Koide of Mukogawa Women's University, in Nishinomiya, and to Dr. Masanosuke Takagi of University of Osaka Prefecture for various discussions.

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*3 In addition the error owing to the drawing figure for the determination of the limiting current may also not be neglected.