Polarographic Studies on Heterocyclic Compounds. II. Saponification of Isonicotinic Acid Methyl Ester

by Yoshinosuke NAGATA and Isamu TACHI

(Received June 30, 1954)

Introduction

In the previous paper(1), polarographic investigations on isonicotinic acid have been carried out and it has been clarified that the limiting current has a character of the kinetic current which is due to the recombination of the dissociated anion of isonicotinic acid with proton. However, if behaviour similar to this acid should be observed also in isonicotinic acid methyl ester, the kinetic current might have to be attributed to some other cause. In this paper, the discussion in the previous paper was confirmed on the basis of the fact that the methyl ester shows behaviour different from the acid. On the other hand, the fact that the methyl ester is saponified in the alkaline medium was found. Since the limiting current of the methyl ester is controlled by diffusion process, the velocity constant of the saponification was determined polarographically from the decrease in the limiting current of the methyl ester. Further, the effects of the temperature and the neutral salt concentration on the velocity constant were estimated by means of the polarographic method.

Experimental Part

Isonicotinic acid methyl ester is provided by Tanabe Pharmaceutical Co. Ltd. It is redistilled at 120°C under reduced pressure (in 25 mm Hg), since it is comparatively unstable in atmosphere and under light.

The buffer solutions used are as follows: McIlvain's buffer solutions (0.1 M Citric acid—0.2 M Sodium phosphate), Kolthoff's buffer solutions (0.1 M Potassium biphosphate—0.05 M Sodium Borate) and Sörensen's buffer solutions (0.05 M Sodium borate—0.1 N Sodium hydroxide).

Capillary constants are $m=1.55$ mg/sec. and $t=3.24$ sec. ($m^{2/3}t^{1/6}=1.63$) in 0.2 N KCl solution at -1.8 v. *vs.* N.C.E., where m and t are the rate of flow of mercury and drop time, respectively. Electrode potentials are referred to the normal calomel electrode and the temperature of the electrolytic solution is maintained at 25±0.5°C.

Experimental Results and Discussion

(1) Effects of pH

A well-defined reduction wave is observed in the acidic and neutral pH range as shown in Fig. 1 (Curve 1). Table I indicates the relationship between pH of the electrolytic solution, the limiting current and the half-wave potential. The half-wave potential shifts to more negative potential with increasing pH value, and the limiting current has a nearly constant value in the acidic and neutral pH range, while in the alkaline side the current gradually decreases with increasing pH value and also with time, and a new second reduction wave appears at the more negative potential than the first one. The second wave is so drawn out (Fig. 1, Curve 2) that the half-wave potential is hardly determinable. At pH 13 (in 0.1 N NaOH), the first wave disappears completely and only the second wave is observed (Fig. 1 Curve 3). Therefore, it is seen that isonicotinic acid methyl ester is decomposed in the alkaline medium and the second wave corresponds to the reduction of decomposition product. Because the second wave is not well-defined, its qualitative estimation is difficult. However, it seems probable that isonicotinic acid methyl ester is hydrolysed by alkali hydroxide as well as general esters. After

TABLE I

RELATIONSHIP BETWEEN pH, THE HALF-WAVE POTENTIAL ($E^{1/2}$) AND THE LIMITING CURRENT (i). 1.06×10^{-3} M ISONICOTINIC ACID METHYL ESTER IN 0.2 N KCl

pH	$E^{1/2}$ (v. *vs.* N.C.E.)	i (μA)
1 (0.1 N HCl)	−0.840	8.77
2.6	−0.885	8.17
3.4	−0.957	8.17
4.4	−0.995	8.10
5.4	−1.055	8.17
6.4	−1.110	8.17
7.5	−1.185	7.97
8.2	−1.230	7.57
9.0	−1.275	7.27
10.1	−1.290	6.60
10.7	−1.290	5.85
13 (0.1 N NaOH)	−1.800*	5.70*

(*); The second wave

All values are measured standing for 30 minutes after prepareation of the electrolytic solutions.

---

1) Y. Nagata and I. Tachi, This Bulletin, 27, 290 (1954).

the hydrolysis of the ester by the action of sodium hydroxide and then neutralization with hydrochloric acid, pH of solution is adjusted to the appointed value. By comparing the half-wave potential of the hydrolysis product with that of isonicotinic acid, a good agreement between these two values is observed as shown in Table II. Therefore, the second wave is due to the reduction of isonicotinic acid. In other words, methyl ester is saponified by alkali hydroxide. At pH 13, it corresponds to the reduction of the dissociated anion of the acid. Hence the second wave in the alkaline pH range is drawn out in consequence of the overlap of the wave of the acid molecule with that of the dissociated anion.

TABLE II

THE HALF-WAVE POTENTIAL ($E_{1/2}$) OF THE HYDROLYSIS PRODUCT OF ISONICOTINIC ACID METHYL ESTER IS COMPARED WITH THAT OF THE ACID. (1) FIRST WAVE, (2) SECOND WAVE

	Hydrolysis Product		Acid	
pH	$E_{1/2}(1)$	$E_{1/2}(2)$	$E_{1/2}(1)$	$E_{1/2}(2)$
9.0	−1.38	—	−1.38	—
10.1	−1.47	−1.80	−1.47	−1.80
10.7	−1.48	−1.81	−1.47	−1.80

(2) Dependence of the Limiting Current on the Height of Mercury Reservoir

When the limiting current in the acidic and neutral pH range increases linearly with the square root of h (h is the height of mercury reservoir), it is controlled by diffusion process (Table III)⁽²⁾. However, as in the case of the alkaline pH range the saponification reaction takes place at the same time, it is necessary to take the reaction into account. Now, if the approximate correction for the decrease in the limiting current of the first wave caused by the saponification is made, the limiting current has a linear realtionship with $\sqrt{h}$ and the slope (of the line that i is) plotted *vs.* $\sqrt{h}$ agrees with that at pH44. Hence the limiting current of the first wave at pH 10.7 is also controlled by diffusion process as well as at pH 4.4. On the other hand, the second wave height, which can be calculated as the difference between the total wave height and the corrected first wave height, since during the measurements the total wave height, which corresponds to the sum of ester and acid, is hardly changed by saponification, changes linearly with $\sqrt{h}$, so that it has been concluded that the limiting current of second wave (the mixed wave of the acid molecule and dissociated anion of isonicotinic acid) is controlled by the diffusion process. However, in the polarogram after the saponification, the limiting current of the saponification product wave is nearly independent of the height of the mercury reservoir (Table IV), so that it has the

TABLE IV

INFLUENCE OF THE HEIGHT OF EHE MERCURY RESERVIOR ON THE FIRST WAVE HEIGHT OF THE SAPONIFICATION PRODUCT OF ISONICOTINIC ACID METHYL ESTER AT pH 10.1

h	i
60	0.570
55	0.555
50	0.570
45	0.555
40	0.540
35	0.555
30	0.540

TABLE III

DEPENDENCE OF THE LIMITING CURRENT INTENSITY ON THE HEIGHT OF THE MERCURY RESERVOIR. 1.06×10^{-3} M ISONICOTINIC ACID METHYL ESTER IN 0.2 N KCl

pH		4.4		10.7			
h	$\sqrt{h}$	i	$i/\sqrt{h}$	i_1	i_2	$i_1/\sqrt{h}$	$i_2/\sqrt{h}$
60	7.74	9.30	1.20	4.86	1.44	0.628	0.186
55	7.42	8.70	1.17	4.65	1.38	0.626	0.186
50	7.07	8.40	1.19	4.53	1.14	0.645	0.161
45	6.71	7.95	1.17	4.21	1.29	0.627	0.192
40	6.32	7.42	1.16	3.99	1.17	0.631	0.185
35	5.91	6.97	1.18	3.84	1.11	0.649	0.187
30	5.48	6.45	1.18	3.54	1.08	0.646	0.197
		av.	1.18		av.	0.636	0.185
		$i/\sqrt{h}C$	1.11		$i/\sqrt{h}C$	1.15	1.13

C denotes the concentration (millimol/litre) of the depolarizer.

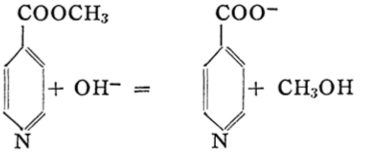
---

2) D. Ilkovič, *Collection Czech. Chem. Communs.*, 6, 498 (1934). I. M. Kolthoff and J. J. Lingane, "Polarography", Interscience Publishers, Inc. New York, N. Y., 1952, p. 44, 85. I. Tachi, "Polarography", Iwanami Book Co. Ltd., Tokyo, 1954, p. 82.

character of the kinetic current(3). Therefore, the idea that the kinetic current of isonicotinic acid is due to the recombination of the dissociated anion of acid with proton is supported.

(3) Saponification of Isonicotinic Acid Methyl Ester

(a) Measurement of the velocity constant.—Assuming that isonicotinic acid methyl ester is saponified by alkali hydroxide in the same way as in general saponification of ester, we may consider that



(1)

Since the saponification reaction takes place in the second order, the reaction velocity of saponification, dx/dt, and the velocity constant, k, are given by

$$\frac{dx}{dt}=k(a-x)(b-x) \tag{2}$$

and

$$k=\frac{2.303}{(b-a)t}\log\frac{a(b-x)}{b(a-x)} \tag{3}$$

respectively, where a and b denote the initial concentrations of isonicotinic acid methyl ester and sodium hydroxide, respectively, and x represents the decrease of each component after time t.

In order to determine the velocity constant, the unreacted amount of each substance at time t, $(a-x)$ and $(b-x)$, must be measured. The concentration of methyl ester can be determined polarographically, while that of sodium hydroxide is impossible. However, since the reaction between ester and sodium hydroxide proceeds one to one, $(b-x)$ value can be calculated from b and $(a-x)$ values. The concentration of the ester is determined by means of the calibration curve which is drawn beforehand in 0.2 N KCl solution. Futhermore, since the values of $(a-x)$ and $(b-x)$ are given as the molar concentration, it is unnecessary to take the kinetic current into account.

J. Heyrovský(4) and others5,6,7), in the case of the determination of the hydrolysis velocity constant, have measured the wave height at a certain time interval, in order to follow the change in the concentration of the reactant with time. In our case, since the reaction velocity is considerably great, the method which has been examined by R. Pasternak(8) is adopted: i. e., the potentiometer drum is used as a timer, and the applied voltage is kept by the aid of another potentiometer at a constant value, where the limiting diffusion current of the ester is oberved.

The electrolytic solution (1.09×10^{-3} M ester in 0.2 N KCl and 2×10^{-3} M NaOH) is prepared rapidly and after hydrogen gas is bubbled through the solution for one minute for the sake of removal of dissolved oxygen in the solution, it is then polarographed immediately. Fig. 2 shows the current-time diagram obtained in this way. The slit lamp line indicates the time interval (the potentiometer drum is rotated in the rate of 28±0.5 sec. per round), hence the wave height at an arbitrary time can be measured from the base line which is obtained in the current-voltage curve of the ester.

Table V gives the velocity constant calculated by inserting the experimental values, which are obtained from Fig. 2, into Eq. (3). In the same way, the velocity constants in the case of the various concentrations of sodium hydroxide are determined (Table VI). When the concentration of sodium

TABLE V

VELOCITY CONSTANT CALCULATED BY THE DATA OF FIG. 2

t (sec.)	$(a-x)\times10^4$ M	$(b-x)\times10^4$ M	k(M/L)$^{-1}$ sec^{-1}
0	6.77	15.87	
50	5.82	14.92	1.951
100	5.02	14.12	2.001
150	4.47	13.57	1.892
200	3.94	13.04	1.893
250	3.43	12.53	1.945
300	3.10	12.20	1.894
350	2.76	11.86	1.900
400	2.48	11.58	1.891
450	2.16	11.26	1.949
		av.	1.924±0.037

TABLE VI

DEPENDENCE OF THE VELOCITY CONSTANT ON THE CONCENTRATION OF SODIUM HYDROXIDE

Conc. of NaOH	k (M/L)$^{-1}$sec.$^{-1}$
2×10^{-3} M	1.924±0.037
3 〃	2.023±0.066
4 〃	2.086±0.086
5 〃	2.013±0.060
7.5 〃	1.957±0.063

---

3) R. Brdička and K. Wiesner, *Collection Czech. Chem. Communs.*, 12, 138 (1947). I. Tachi, "Polarography" Iwanami Book Co. Ltd., Tokyo, 1954, p. 107.

4) J. Heyrovsky and I. Smoler, *Collection Czech. Chem. Communs.*, 4, 521 (1932).

5) R. Brdička, *J. Gen. Physiol.*, 19, 899 (1936).

6) R. Pasternak and H. v Halban, *Helv. Chim. Acta*, 29, 190 (1946).

7) H. H. G. Jellinek and A Gordon, *J. Phys. and Colloid Chem.*, 53, 986 (1949).

8) R. Pasternak, *Helv. Chim. Acta*, 30, 1984 (1947).

hydroxide is higher than 10^{-2} M, the reaction rate is so great that we can not follow the decrease of the ester polarographically. It is concluded from the data in Tables V and VI that the saponification of the ester proceeds in the second order, and the average velocity constant is equal to 1.924 $(\mathrm{M/L})^{-1}$ sec^{-1}.

(**b**) **Effect of the Concentration of the Neutral Salt on the Velocity Constant.**—In general, the reaction rate in the solution is influenced by the presence of neutral salt. The neutral salt effect is caused by the fact that, by addition of neutral salt, in the case of ionic reaction the ionic strength is varied (primary salt effect), or when one of reaction substances is a weak electrolyte the dissociation equilibrium is effected (secondary salt effect). As shown in Table VII, though the velocity constant can not be determined polarographically under the condition without neutral salt, it seems probable that the velocity constant is not affected by the nature and concentration of neutral salt. It may be due to the fact that the saponification reaction takes place between molecule and ion.

TABLE VII

EFFECT OF THE NATURE AND CONCENTRATION OF THE NEUTRAL SALT ADDED
1.09×10^{-3} M ESTER IN 0.002 M NaOH

Conc. of salt	k $(\mathrm{M/L})^{-1}$ $\mathrm{sec.}^{-1}$
0.2 N KCl	1.924 ± 0.037
0.5 N 〃	1.987 ± 0.096
1 N 〃	1.991 ± 0.076
0.5 N NaCl	2.027 ± 0.054
〃 +0.5 N KCl	1.819 ± 0.070

(**c**) **Effect of the Temperature on the Velocity Constant.**—It is clear by the data in Table VIII that the velocity constant increases considerably with rising temperature. The influence of the temperature on the velocity constant is expressed by Arrhenius equation.

$$k=Ae^{-E/RT} \qquad (4)$$

where E, R, T and A are the energy of activation, gas constant, absolute temperature and frequency factor, respectively.

TABLE VIII

INFLUENCE OF THE TEMPERATURE ON THE VELOCITY CONSTANT 1.06×10^{-3} M ESTER IN 0.2 N KCl AND 2×10^{-3} M NaOH

t° C	k $(\mathrm{M/L})^{-1}$ shc^{-1}.
25	1.924 ± 0.037
35	3.433 ± 0.120
44	6.690 ± 0.514
53	11.230 ± 1.303

From Eq. (4), it follows that

$$\log k=-\frac{E}{2.303\,RT}+\text{const.} \qquad (5)$$

This indicates that the plot of $\log k$ against $1/T$ should be a straight line, whose tangent gives the energy of activation. From the tangent of the straight line in Fig. 3 which is plotted by means of the data in Table VIII, it is found that the energy of activation is equal to 12 kcal.

Summary

(1) Isonicotinic acid methyl ester gives a single reduction wave and the half-wave potential shifts to more negative potential with increasing pH.

(2) Isonicotinic acid methyl ester is saponified in the alkaline medium and the velocity constant of saponification is determined polarographically on the basis of the second order reaction equation.

(3) The velocity constant is scarcely influenced by the addition of neutral salts, but increases with rising temperature. The activation energy of saponification is calculated according to the Arrhenius equation.

The authors wish to express their thanks to Tanabe Pharmaceutical Co. Ltd., which furnished the specimen, and also to the polarographic group, to which they belong, for their helpful discussion.

Department of Agricultural Chemistry,
Faculty of Agriculture, Kyoto
University, Kyoto