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ELECTROCHEMISTRY OF DIHALOGENATED NICOTINIC ACIDS IN AQUEOUS AND APROTIC MEDIA

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ABSTRACT

The electrochemical reduction of several 2,5- and 5,6- dihalonicotinic acids have been studied in dimethyl sulfoxide as well as in aqueous buffers of different pH. The polarographic half-wave potentials for the reduction of these compounds in both media are reported here. The compounds appear to reduce at the carboxyl group. The presence of halogen atoms on the pyridine ring facilitates reduction.

INTRODUCTION

The synthesis and spectroscopic (IR and NMR) characterization of several 2,5- and 5,6- dihalonicotinic acids have been reported earlier (Setliff, 1970, 1972, 1973, 1976 and 1978). Because of the chemical similarity with vitamin B (niacin), these compounds are of important biological significance. Since biological activities of chemical agents are generally believed to occur via oxidation-reduction mechanism, it is essential that the redox properties of these compounds be determined in order to understand the molecular basis of such activities. No electrochemical studies of nicotinic acid and its halogen derivatives have yet been reported. We have therefore undertaken the task of determining the polarographic half-wave potentials for the reduction of these compounds in both protic and aprotic media. In this report, the results obtained in dimethyl sulfoxide and in aqueous buffers are presented.

EXPERIMENTAL

Reagents: Dimethyl sulfoxide (DMSO) and tetrabutylammonium perchlorate (TBAP) were of analytical grade (Fisher Chemicals) and were used without further purification. Aqueous buffers of various pH were prepared (Carmody, 1961) from analytical grade boric acid, citric acid and trisodium phosphate (Fisher Chemicals). The aqueous reaction media were 0.1M buffer solutions, whereas the aprotic medium was a solution of 0.1M TBAP in DMSO, which was dehydrated (commercial TBAP and DMSO contain water) prior to use by passing over basic alumina (Woelm).

Apparatus: The half-wave potentials were determined by Differential Pulse Polarography using a three-electrode polarographic analyzer (Model PAR 174A; Princeton Applied Research Corporation, Princeton, NJ). The cathode, the counter-electrode and the reference electrode were dropping mercury electrode (DME), platinum foil and saturated calomel electrode (SCE) respectively. In aprotic medium, however, a low-porosity calomel, filled with 0.40M tetraethylammonium chloride to adjust voltage to 0.00 volt vs. SCE, was used as reference to minimize water-leakage into the medium. The polarograms were recorded on an X-Y recorder (Model 2200 Omnigraphic; Houston Instruments, Austin, TX). The mercury drop-rate of the DME was controlled by a mechanical drop-timer (Princeton Applied Research Corporation). The temperature of the reaction medium was maintained at $25.0 \pm 0.1^\circ\text{C}$.

Procedure: Twenty ml of the solution was poured into the reaction vessel, purged with ultra-high purity argon for thirty minutes to remove dissolved oxygen and a differential pulse polarogram of the medium (background) was taken using the following conditions: Initial Potential = 0.00 volt vs. SCE, Potential Scan Rate = 5 mV/sec, Pulse

Amplitude = 25mV and Drop Time = 1.0 sec. During potential scan in the negative direction (reduction), the solution was quiescent and the argon flow was diverted above the solution to keep atmospheric oxygen and moisture away. To the solution, about five mg of a particular compound was then added, stirred to dissolve completely, and the polarogram was taken under the same condition as above. The procedure was repeated for other compounds.

RESULTS AND DISCUSSION

The technique of Differential Pulse Polarography (DPP) is superior to that of Direct Current Polarography (DCP) for the determination of half-wave potentials due to improvement of signal to noise ratio as a result of discrimination against capacitative current (Bond, 1984). Moreover, polarograms obtained by DPP show Gaussian peaks due to charge-transfer process, compared to sigmoidal curves in DCP, and can be evaluated more precisely. In DPP, the half-wave potential ($E_{1/2}$), which is characteristic of a particular electroactive compound and is a measure of its ability to be either oxidized or reduced, can be related to the peak potential (E_p) of the polarogram by the equation:

$$E_{1/2} = E_p \pm \Delta E/2$$

where ΔE = pulse amplitude and '+' and '-' signs refer to reduction and oxidation processes respectively.

Figure 1 shows typical polarograms obtained by DPP in DMSO for nicotinic acid and two of its dihalogenated derivatives, namely, 5-chloro-6-iodo- and 6-chloro-5-iodo- nicotinic acids. Each polarogram displays two distinct peaks, indicating that the compounds are undergoing reduction in two steps. A previous report (Lund, 1983) showed that in acetonitrile, an aprotic medium, the electrochemical reduction of pyridine ring is very difficult. The two peaks, therefore, can be attributed to reduction of the carboxyl group.

The half-wave potentials obtained for a number of dihalonicotinic acids in both protic and aprotic media are shown in Table 1. While each compound showed two peaks in DMSO, additional peaks were observed in aqueous media, especially at a lower pH. This may indicate that in aqueous media either the protonated nitrogen of the pyridine ring or halogen atoms on the ring are also reduced. The presence of halogen atoms on the ring also have profound effect on the half-wave potential for the reduction of carboxyl group (see Figure 1 and Table 1). Both in aqueous and aprotic media, the first $E_{1/2}$ is shifted to a more positive value, as compared to that of the unsubstituted nicotinic acid, indicating that halogen atoms facilitate reduction. This positive shift of $E_{1/2}$ can be explained in terms of counter-balancing inductive effect (-I) and resonance effect (+R) of aryl halogen substituents (Gould, 1959). Because of this opposing action, the net electron-withdrawing capacity of halogens is in the order: $\text{I} > \text{Br} > \text{Cl} > \text{F}$.

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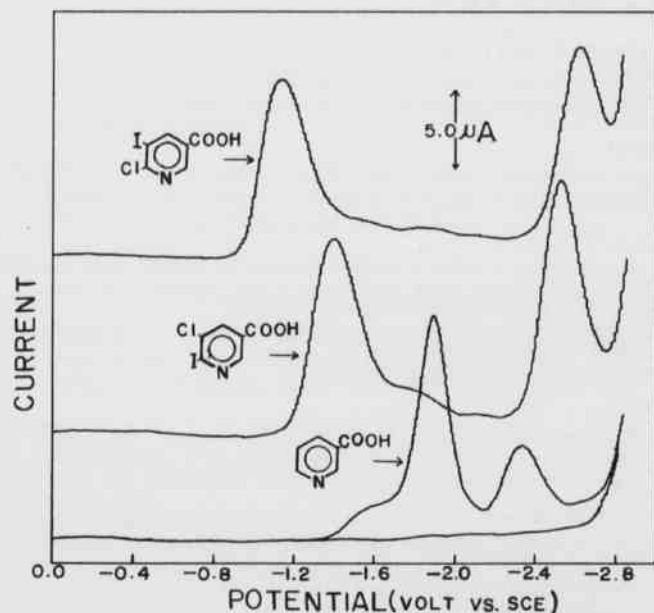


Figure 1. Differential Pulse Polarograms of nicotinic acid and its dihalogenated derivatives in 0.10M TBAP/DMSO. Conditions: scan rate = 5mV/sec, pulse amplitude = 25 mV, drop time = 1.0 sec. The bottom curve (flat) represents the background.

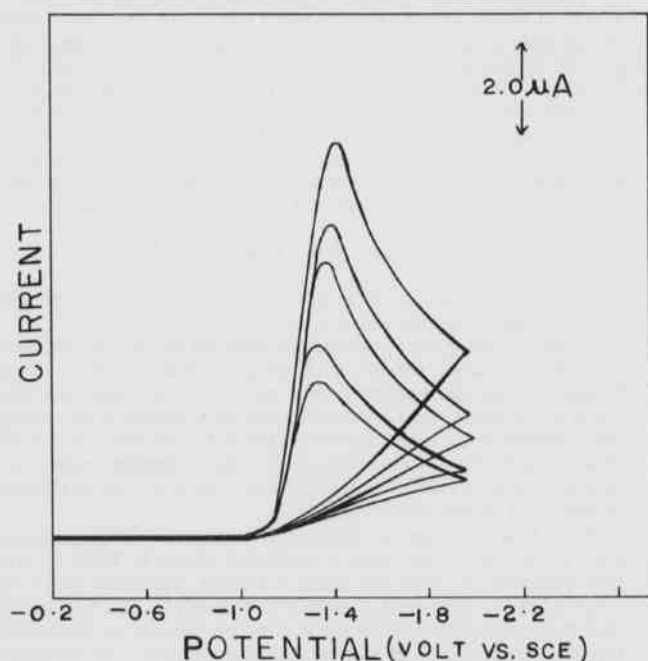


Figure 2. Cyclic Voltammograms of 5-Chloro-6-iodo-nicotinic acid in 0.10M TBAP/DMSO at potential scan rates of 10, 20, 50, 100 and 200 mV/sec. The peak height increases with scan rate.

I and Br at 5- and 6- positions of the pyridine ring therefore favor reduction of the carboxyl group. In DMSO, a negative shift of the second

Table 1. Half-Wave Potentials for Reduction of Some Dihalonicotinic Acids in DMSO and in Aqueous Buffers

Compound (Nicotinic Acid)	$E_{1/2}$ in DMSO (Volt vs. SCE)	$E_{1/2}$ in Water (Volt vs. SCE)		
		pH 2.0	pH 4.0	pH 6.0
Unsubstituted	-1.92 -2.36	-1.05 -1.14	-1.05 -1.13	-1.05 -1.22
5-chloro-6-iodo-	-1.38 -2.51	-0.32 -0.86 -1.09	-0.44 -1.21 N.D.	-0.61 -1.37 N.D.
6-chloro-5-iodo-	-1.14 -2.62	-0.69 -1.07 -1.16	-0.80 -0.90 -1.24	-1.01 -1.09 N.D.
2-chloro-5-iodo-	-1.57 -2.43	-0.83 -1.12	-1.11 -1.37	-1.33 -1.45
2-bromo-5-iodo-	-1.35 -2.43	-0.75 -1.08 -1.15	-0.93 -1.25 N.D.	-1.26 -1.61 N.D.
5-bromo-6-iodo-	-1.34 -2.47	-0.31 -0.85 -1.09	-0.43 -0.99 -1.19	-0.57 -1.38 N.D.
6-bromo-5-iodo-	-1.09 -2.53	-0.59 -0.66 -1.13	-0.72 -1.23 N.D.	-0.92 -1.14 N.D.
5,6-dibromo-	-1.50 -2.47	-0.60 -0.85 -1.09	-0.73 -0.99 -1.19	-1.03 -1.38 N.D.
2,5-dibromo-	-1.49 -2.49	-0.81 -0.93 -1.13	-1.01 -1.23 N.D.	-1.36 N.D. N.D.
2,5-dichloro-	-1.59 -2.44	-0.94 -1.11	-1.29 -1.51	-1.42 N.D.
5,6-dichloro-	-1.57 -2.41	-0.68 -0.85 -1.11	-0.86 -1.10 -1.23	-1.13 -1.23 -1.35

* Half-wave potentials are given in each column in sequence of First $E_{1/2}$, Second $E_{1/2}$ etc.

N.D. = The peak corresponding to the half-wave potential is in existence but is not clearly detectable.

$E_{1/2}$ was generally observed (see Table 1), indicating greater difficulty of further reduction of the compounds. The reason for such a shift is not clearly understood, although it appears that solvent (DMSO) molecules may play an important role.

Figure 2 shows typical cyclic voltammograms obtained for halogenated nicotinic acids in DMSO at various potential scan rates. The initial reduction of the compound is followed by a rapid chemical reaction (EC mechanism) of the product with solvent molecules. As a result, the product cannot be reoxidized back to the original compound during reverse scan. Similar behavior was also observed in aqueous media.

From Table 1, it is also obvious that the pH of the aqueous media has a profound effect on the relative ease of reduction of the carboxyl group. At lower pH, the half-wave potential shifts to the positive direction, showing the protons are involved in the reduction process. Similar proton-mediated reduction of isonicotinic acid has been reported earlier (Lund, 1963). In dry DMSO, however, the absence of protons dictates that the mechanism of reduction may be totally different from that in aqueous medium and most likely the reduction proceeds through a free-radical mechanism. The reaction products in two solvents may therefore be quite different. Caulometric analysis of the reduction processes in both media, followed by isolation and gas-chromatographic identification of the products, are now in progress in our laboratory to fully understand the mechanism of reduction of these biologically important compounds.

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