ELECTROCHEMICAL BEHAVIOUR OF 3-PYRIDYL-N,N-BIS-[(8-QUINOLYL)AMINO]METHANE

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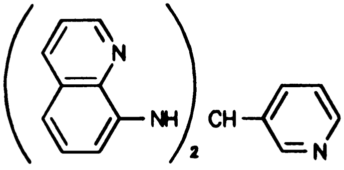
3-Pyridyl-N,N-bis[(8-quinolyl)amino]methane was studied by DC polarography, coulometry, cyclic voltammetry and differential pulse polarography in a system comprising Britton–Robinson buffer and 15 vol.% ethanol at pH 7.0. The nature of the waves was investigated, and the reduction mechanism is suggested. DPP was also used for a quantitative determination of the substance, and a limit of detection of 3 μmol l^{-1} was obtained.

3-Pyridyl-N,N-bis[(8-quinolyl)amino]methane (PQAM) is a novel[1] alkylating agent which possesses potential antineoplastic properties. Polarography and voltammetry are convenient techniques to gain insight into the structure and properties of cytostatics[2 – 8]. PQAM has not been so far investigated electrochemically but the substance is known to contain two quinoline moieties and one pyridine moiety, and electrochemical studies of quinoline, pyridine and related compounds exist[9 – 14]. There are three electroactive groups in PQAM, three C=N double bonds which take part in electrodic reduction. This is a structure which arouses great interest.



PQAM

EXPERIMENTAL

Polarographic and voltammetric measurements were carried out with an Amel 473 multipolarograph analyzer. Chronocoulometric examinations were carried out using a system of standard Amel instruments comprising a potentiostat 549, a function generator 566, an interface unit 560A and an integrator 721. Both systems were interfaced to a time-base Amel 863 X-Y recorder. The pH values were measured with a Radiometer pH meter model 62 possessing an accuracy of ±0.02. Temperature was controlled by means of a Techne thermostatic bath composed of a RB-5 refrigerated bath and a TE-8A thermoregulator; the temperature stability was ± 0.05 °C at 40 °C.

A Metrohm mercury capillary electrode served as the working electrode for DC polarography. Its parameters were m = 7.26 mg s^{-1} and t = 3.20 s at −1.1 V (vs SCE) in the Britton–Robinson buffer–15 vol.% ethanol system at pH 7.0, an ionic strength of 0.1 mol l^{-1} and a mercury reservoir height of 45 cm. In differential pulse polarography, the working electrode drop time was approximately twice that of the DC polarography mercury drop time. The working electrode used for voltammetry was a Metrohm 6.0335.000 hanging mercury drop electrode with a mercury electrode area between 1.95 and 2.95 mm^2. A mercury pool electrode was employed as the coulometric working electrode. A saturated calomel electrode (SCE) and a platinum electrode, both by Ingold, were used as the reference and auxiliary electrodes, respectively.

The PQAM is a novel compound synthesized in the Organic Chemistry Department of the Alcalà de Henares University[1]. All other chemicals were of reagent grade purity. Mercury was first purified chemically and subsequently distilled at a reduced pressure.

Being insoluble in water but soluble in alcohol, PQAM was dissolved in ethanol and subsequently diluted with the aqueous solution so that the final ethanol content was 15 vol.%. The solutions to be measured were prepared using 3.75 ml of PQAM solution in ethanol, 10 ml of Britton–Robinson buffer (pH 7.0) in each 25 ml cell, and the ionic strength was adjusted to 0.1 mol l^{-1} with KCl. The solutions were allowed to stand for several hours because the polarograms were first time dependent and only later their shape established, presumably due to the slow dissolution.

All measurements were performed under nitrogen at 25 °C.

RESULTS AND DISCUSSION

DC Polarography

PQAM in the buffer solution with 15 vol.% ethanol at pH 7.0 exhibits four waves at approximately −1.0, −1.3, −1.6, and −1.8 V, respectively (Fig. 1).

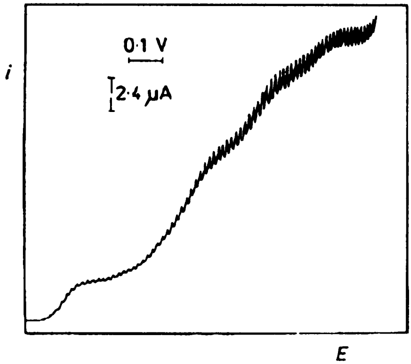


FIG. 1

DC polarogram of PQAM (0.51 mmol l^{-1}) in a system comprising Britton–Robinson buffer and 15

The first wave is diffusion controlled, the limiting current varies linearly with concentration (Fig. 2) and with the mercury column height square root. The diffusion current constant obtained is 2.26, temperature coefficient 2.3% K^{-1}. Logarithmic analysis of the *i–t* curves gave slopes ranging from 0.13 to 0.20.

The second wave looks like two overlapping waves (Fig. 1) and has a mixed diffusion-kinetic-adsorption nature. The limiting current increases linearly with concentration up to approximately 0.5 mmol; at higher concentrations the current tends to level to a limiting value (Fig. 2). With increasing concentration, the slopes of the $\log i$ vs $\log [H]$ plots change from 0.28 to 0.61 and the wave loses its kinetic character and acquires more of an adsorption character; the temperature coefficient is 1.7% K^{-1} and the logarithmic analysis of the *i–t* curves gives slopes from 0.22 to 0.32.

The heights of the third and fourth waves decrease with increasing PQAM concentration (Fig. 2). Observed for a quinoline compound, behaviour of this kind has been attributed to catalytic hydrogen discharge[11]. Since PQAM has two quinoline parts, we suggest that the third and fourth waves are catalytic hydrogen waves and we are not going to deal with them in this paper.

Coulometry

The number of electrons exchanged was determined by controlled potential coulometry. The solution was electrolyzed at a controlled potential corresponding to the limiting current of the first wave. The *Q–t* curves were recorded continuously during the electrolysis until the wave vanished completely. The background current was discriminated by extrapolation, i.e. by extending the linear segment of the curve until it crossed the *Q*-axis. The results obtained ranged between 1.76 and 2.18. The number of electrons was also determined by monitoring the decrease of the wave at different

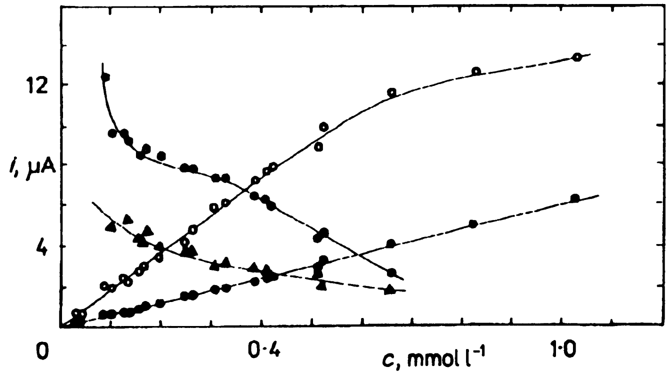


Fig. 2

Dependence of the DC limiting current on PQAM concentration. Britton–Robinson buffer–15 vol.% ethanol, pH 7.0. Wave: ● 1st, ○ 2nd, ◑ 3rd, ▲ 4th times, and the results obtained lay between 1.70 and 2.28. So, we conclude that the first wave corresponds to a two-electron process. The number of electrons transferred in the process giving rise to the second wave could not be determined due to its mixed diffusion-kinetic-adsorption nature.

Mechanism

PQAM contains three electroactive groups, three N=C double bonds, one N=C double bond in the pyridine part, and two N=C double bonds in the two quinoline parts of the molecule.

In experiments in the medium used in this study, quinoline was discharged at −1.1 V but no pyridine reduction wave was observed, although such a wave was detected in unbuffered KCl supporting electrolyte medium at −1.65 V.

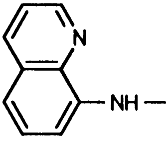
For quinoline and pyridine, the lowest empty molecular orbital (LEMO) energies are -0.7283 and 0.3416, respectively, the N=C bond orders are 1.55 and 1.42, respectively, the Mulliken negative charge on N are 0.295 and 0.308, respectively, and the MOPAC negative charges are 0.241 and 0.251, respectively. These values can account for the above facts.

With the most stable PQAM configuration, the LEMO energies are -0.7209, -0.6535 and -0.1748, the N=C bond orders are 1.56 and 1.55 for the two quinoline rings and 1.43 for the pyridine ring, the Mulliken negative charges on N are 0.282 and 0.294 for the two quinoline rings and 0.311 for the pyridine ring, and the MOPAC negative charges are 0.229 and 0.240 for the two quinoline rings and 0.253 for the pyridine ring. So, the quinoline ring N=C double bonds in PQAM are more easily reduced than the pyridine ring N=C double bond.

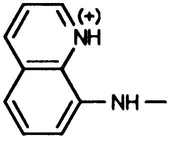
Taking into account the above facts along with published data[9,12 - 14], we suggest that the first and second waves are due to the reduction of the quinoline N=C double bonds in the protonated [$(RH^+)_2P$] and non-protonated (R_2P) species, respectively. The reduction of the N=C double bond in the pyridine ring is obscured by the backround current.

The following mechanism is suggested:

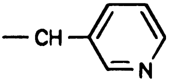
$$(RH^+)_2P \xrightleftharpoons{e} (RH^+)P(RH) \xrightleftharpoons{e} \begin{matrix}(RH^+)P(RH^-)\\(RH)_2P\end{matrix} \xrightarrow{X} A$$



R



RH⁺



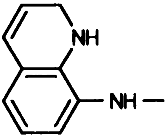
P

First wave:

The quinoline N=C double bond is the reduced moiety, but the two electrons can enter either different N=C bonds to give rise to $(RH)_2P$ or the same N=C bond to give rise to $(RH^+)P(RH^-)$. If both electrons enter the same bond, X can be one of three species: It can be an H^+, whereupon $(RH^+)P(RH_2)$ is the reduction product; or it can be another molecule of the electroactive substance, resulting in a dimer; or it can be another group from the same molecule, wherupon an intramolecular bond arises. If each electron enters an N=C bond, an intermolecular or an intramolecular bond can be formed.

Second wave:

The pathway is as for the first wave but proceeds from non-protonated PQAM, until the formation of A and further to $(RH_2)_2P$.



RH_2

Cyclic Voltammetry

In cyclic voltammograms using a new mercury drop and in the first scan, PQAM exhibits three cathodic peaks but no anodic peaks. As in the polarographic study, only the first two peaks were studied. The height of the first cathodic peak $i_{p,1}$ varies linearly with the concentration of PQAM, the electrode area, and the scan rate square root. The potential peak becomes more negative with increasing scan rate, indicating a simple irreversible charge transfer. The height of the second cathodic peak $i_{p,2}$ varies linearly with the electrode area and with the scan rate, and also with the PQAM concentration up to 0.2 mmol l^{-1} but at higher concentrations the shape is nonlinear. The potential peak becomes more negative with increasing scan rate, which can be due to adsorption with reactant adsorbed; this is consistent with the results of the DC polarographic investigation.

Differential Pulse Polarography

The dependence of the height, shape and position of the differential pulse polarographic peak on the scan rate, pulse amplitude, drop time and electrode area were examined with a view to establishing the optimum conditions for analytical determination.

A scan rate of 2 mV s^{-1}, a pulse amplitude of 50 mV, a drop time of 1 s and an electrode area of 2.54 mm^2 (mercury column height of 45 cm) were selected.

The calibration curve was linear for both peaks. The first peak had a slope of 0.0327 μA l μmol^{-1} and intercept of −0.082 μA, and a fitting regression coefficient of 0.999 (0.99 over the concentration range of 1 – 40 μmol l^{-1}) was obtained. The mean value of the $i_{p,1}/C$ constant was 0.026 μA μmol^{-1} l with a standard deviation of 0.0018. At concentrations lower than 3 μmol l^{-1} the signal is distorted, and so the value of 3 μmol l^{-1} is regarded as the detection limit for PQAM.

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