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PRELIMINARY NOTE

Electrochemical properties of nicotinamide derivatives in aqueous solution

Part IV. Oxidation of N₁-alkyl-1,4-dihydronicotinamides

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The electrochemical reduction of nicotinamide–adenine-dinucleotide (NAD⁺) and model compounds has been extensively studied^{1–3}; on the other hand very few papers have been published on the electrochemical oxidation of nicotinamide–adenine-dinucleotide reduced (NADH) in aqueous solution. Haas⁴ reported the occurrence of an oxidation wave of NADH at pH 8.6 at rotating platinum and glassy carbon disk electrodes (with respective half-wave potentials 0.90 ± 0.02 and 0.67 ± 0.03 V vs. NHE); macroscale electrolyses lead to NAD⁺ by a two-electron oxidation^{4,5}. In this paper we shall present the features of the electrochemical oxidation of model compounds of NADH, namely N₁-benzyl- and N₁-propyl-1,4-dihydronicotinamide (NBzNH and NPrNH) in aqueous solution, buffered within a large pH range; a possible mechanism is deduced from these data. Extensive studies have shown the occurrence of a “primary acid modification” of aqueous NADH solutions or its models below pH 7 (ref. 6); the common explanation put forward is a saturation of the 5–6 double bond in the pyridinic ring, the u.v. absorption band being shifted from 355 to 290 nm. Therefore the results and discussions presented here only concern the pH range 7 to 13.

Experimental

All products used were prepared in this laboratory, according to published methods, namely NBzN⁺Cl[−] (ref. 7), NBzNH and NPrN⁺Br[−] (ref. 8), NPrNH (ref. 9). The purity and concentration of the freshly prepared aqueous solutions were checked by u.v. spectrophotometry with a Cary 14 apparatus. Drop-time controlled polarography and voltammetry were carried out with Tacussel equipment (PRT 500 LC, Servovit 9 B, S6 RZ millivoltmeter) and a Sefram “Luxytrace” bigalvanometric recorder. A Tacussel IG 4-100 electronic integrator was used for coulometry. At the beginning of all macroelectrolyses a Fontaine A 60 power-supply was connected between the counter-electrode and the generator. All aqueous solutions were thermostated at $25.0 \pm 0.1^\circ\text{C}$ during the experiments.

Electrochemical properties of NBzNH

NBzNH displays a single oxidation wave at rotating platinum (Fig. 1, curve 1), gold and glassy carbon electrodes; the half-wave potential values are respectively 0.66 ± 0.02 , 0.60 ± 0.025 and 0.48 ± 0.04 V *vs.* NHE. The anodic and cathodic potential sweeps were performed in the 0.2–1.2 V *vs.* NHE range. Thus all $E_{1/2}$ values given refer to the anodic potential scan. This half-wave potential depends neither on pH (in the range 7 to 13) nor on the NBzNH concentration in the range 5×10^{-5} to 5×10^{-4} M. The maximal limiting current is pH-independent and proportional to the concentration of NBzNH in the same ranges of pH and concentration. The slope of the wave is rather small: $E_{3/4} - E_{1/4}$ equals 90 to 120 mV with the above-mentioned electrodes. No cathodic peak is observed during a rapid return potential scan (4 V s^{-1}) in cyclic voltammetry experiments (platinum and glassy carbon disk electrodes). These observations involve the irreversibility of the electrochemical oxidation process.

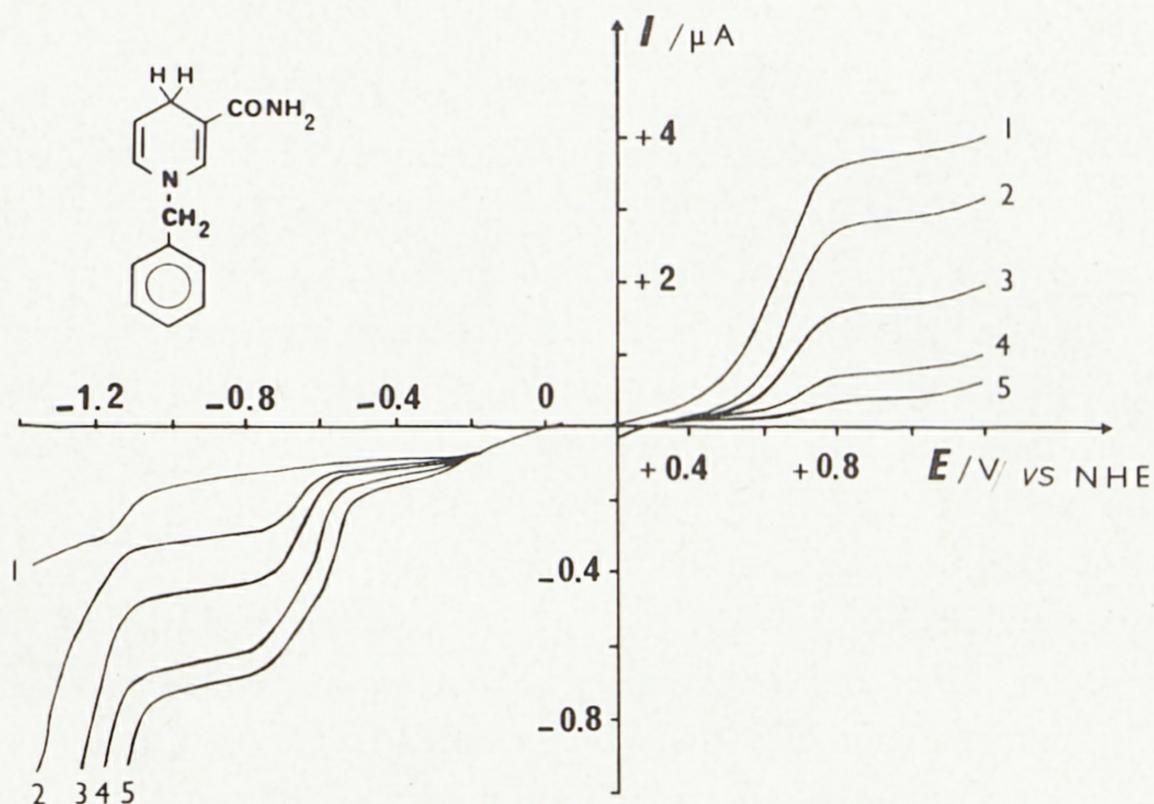


Fig. 1. Current–potential curves of an aqueous 5×10^{-4} M N_1 -benzyl-1,4-dihydronicotinamide solution (buffered at pH 8.3) by voltammetry at a rotating platinum disk electrode (anodic part) and drop-time controlled polarography (cathodic part), during a macroscale electrolysis at +0.85 V *vs.* NHE. (1) Initial solution; (2) solution after 0.25, (3) 0.50, (4) 1.0 and (5) 1.2 moles of electrons/mole electrolysis.

Comparisons of voltammetric wave heights with known oxidizable compounds suggest a two-electron process. This is confirmed by cathodic and anodic scans at a rotating glassy carbon electrode with a mixture of $NBzN^+$ and NBzNH at the same concentration. The ratio of the heights of the oxidation wave of NBzNH and the reduction one-electron wave¹⁰ of $NBzN^+$ was found to be 2:1.

Furthermore NBzNH solutions present a small cathodic wave at -1.09 ± 0.03 V *vs.* NHE in the 8–10 pH range; its height is in the ratio 1 to 5 with that of equally concentrated $NBzN^+$ (Fig. 1, curves 1 and 5).

Electrochemical properties of NPrNH and NADH

The features of the voltammetric oxidation wave of NPrNH are identical to those of NBzNH: the curves registered in the 8–9 pH range present equal half-wave potentials, slopes and limiting currents. Comparative experiments conducted with NADH solutions at pH 9.5 gave an oxidation wave of identical half-wave potential; however, the limiting current is much weaker, this fact being probably due to the bulkiness of the NADH molecule and/or to some limitation by adsorption reactions.

Total oxidation of NBzNH

Several macroelectrolyses were conducted in $5 \times 10^{-4} M$ aqueous solutions, buffered at pH 8.2, with a platinum gauze electrode at a controlled potential of 0.85 V vs. NHE. During the course of the macroelectrolyses, analyses of the solution were performed through drop-time controlled polarography and voltammetry at a rotating platinum disk electrode (Fig. 1) and through u.v. spectrophotometry (Fig. 2). According to our previous measurements¹¹ on aqueous NBzN⁺ solutions we can conclude that this compound is produced with a yield close to 100% although a small unelucidated reduction prewave appears during the electrolysis (Fig. 1, curves 2 to 5). During the experiments the quantity of disappeared NBzNH is equal to the quantity of formed NBzN⁺, both quantities being proportional to the charge consumed. In spite of numerous attempts to achieve reproducible results, the ratio moles of electrons/mole remained scattered between 1.2 and 1.9, the mean value being 1.55.

Total chemical oxidation of $5 \times 10^{-4} M$ NBzNH solutions was performed using

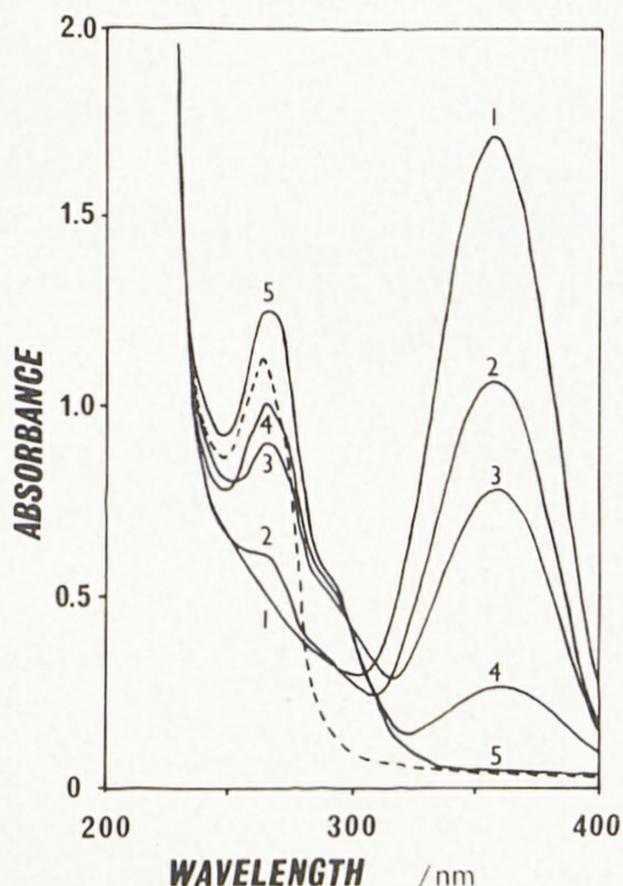


Fig. 2. U.v. spectra of an aqueous $5 \times 10^{-4} M$ N₁-benzyl-1,4-dihydronicotinamide solution (buffered at pH 8.3) during a macroscale electrolysis at +0.85 V vs. NHE. (1) Initial solution; (2) solution after 0.25, (3) 0.50, (4) 1.0 and (5) 1.2 moles of electrons/mole electrolysis. (---) Pure NBzN⁺Cl⁻ in aqueous $5 \times 10^{-4} M$ solution in the same buffer.

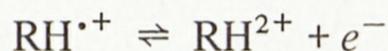
ferricyanide in borate and tris buffers at pH 8.2; NBzNH disappears rapidly and completely as shown by u.v. spectrophotometry. The NBzN⁺ produced is identified by polarography; the increase in its concentration equals the decrease in NBzNH concentration and is proportional to the quantity of ferricyanide added. In spite of several attempts to achieve reproducible results, the number of ferricyanide molecules required for the total oxidation of one NBzNH molecule varied from one experiment to another between 1.2 and 2.0. Further experiments are in progress to elucidate the dispersion of results obtained during total electrochemical and chemical oxidation.

Discussion

NBzNH and NPrNH present a single two-electron oxidation wave whose half-wave potential and limiting current are pH-independent; thus no proton exchange occurs soon before or after the electron exchange. A plausible mechanism could be a somewhat slow reaction



followed by the rapid loss of another electron



and then by a slow deprotonation giving R⁺.

This electrochemical oxidation mechanism of RH differs from the reverse reduction of R⁺ which involves a rapid dimerization of the free radical R[•] (ref. 11).

The comparison between the half-wave potentials of RH oxidation (+0.5 to 0.7 V vs. NHE) and of R⁺ reduction (−0.6 to −0.8 V vs. NHE) demonstrates that it is nonsense to measure zero-current potentials of mixtures like NAD⁺/NADH without chemicals or biochemicals used as mediators. On the other hand ferricyanide and suspensions of aniline-black completely oxidize NBzNH, though their equilibrium potentials are several hundreds of millivolts smaller than the half-wave potential of NBzNH oxidation. An explanation for this discrepancy between electrochemical and chemical behaviour has not yet been found.

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