

Article

The Cathodic Cleavage of the Nitrobenzoyl Group from Protected Aliphatic Amines in N,N-Dimethylformamide

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A redução eletroquímica de aminas alifáticas protegidas pelo grupo 4- e 3-nitrobenzoila em N,N-dimetilformamida foi estudada. Os compostos são reduzidos em duas etapas catódicas. A primeira em aproximadamente -1 V vs. ECS ocorre com a formação de radicais ânions relativamente estáveis, envolvendo a transferência de um elétron. A redução ao diânion ocorre no intervalo de -1,5 e -2,0 V vs. ECS por um processo ECE, conduzindo à clivagem da ligação CN com rendimentos acima de 50%.

The electrochemical reduction of aliphatic amines protected by the 4- and 3- nitrobenzoyl group in N,N-dimethylformamide was reported. The compounds are reduced in two cathodic steps. The first one at about -1 V vs. SCE occurs with the formation of the rather stable anion radicals, involving one electron transfer. The reduction to dianion occurs at potentials between -1.5 and -2.0 V vs. SCE by an ECE process and leads to cleavage of the CN bond in yields above 50%.

Keywords: nitrobenzoyl group, cathodic cleavage, aliphatic amines

Introduction

The electrochemical cleavage method¹⁻⁶ has been an excellent alternative to chemical methods for the removal of reducible protecting groups from amine and alcohol functionalities in polyfunctional molecules. Unfortunately, many commonly used protecting groups reduce only at very negative potentials (above -2 V vs. SCE), resulting in other difficulties which diminish selectivity. One of these protecting groups, the benzoyl group, can be removed by CN bond cleavage of the amides, giving amine with yields of 60 to 90%⁷. The increase of the electron affinity of the protecting group with consequent decrease of the reduction potential can be done by the introduction of the electron acceptors at definite sites of the group.

However few studies related to the electrochemical reduction of aliphatic benzamides modified by introduction of the electron withdrawing substituents into the benzoyl group, in aprotic medium, are reported in the literature^{7,8}. In these papers, where the compounds 2 and 3-cyanobenzamide were studied in N,N-dimethylformamide, it was

ascertained that the reduction occurs through CN bond cleavage giving ammonia.

So, the aim of this work is to study the mechanism of the reduction of N-N-butyl-4- and 3-nitrobenzamide to evaluate the feasibility of removing the nitrobenzoyl group from amine by the electrochemical method.

Experimental

N-N-butyl-4-nitrobenzamide (I) and N-N-butyl-3-nitrobenzamide (II) were prepared from the corresponding nitrobenzoyl chloride and N-butylamine following a literature procedure and recrystallised⁹⁻¹¹. The melting points found were consistent with the published values. The products were also checked by IR and NMR spectroscopy. The electrolyte Bu₄NBF₄, was prepared from Bu₄NHSO₄ and NaBF₄ and recrystallised from ethanol and water¹². The N,N-dimethylformamide (DMF) used was 99.8%, A.C.S. reagent (Aldrich) being kept for 48 h on activated molecular sieves (4 Å) before use.

The electrochemical measurements were made using a potentiostat/galvanostat (PARC model 173), a function

Table 1. Cyclic voltammetric parameters of 1 mmol dm⁻³ nitrobenzamides in DMF/Bu₄NBF₄ (0.1 mol dm⁻³) at a glassy carbon electrode.

Benzamides	Potential scan rate V s ⁻¹	1st reduction process			2nd reduction process		
		-E _{pc} V vs. SCE	I _{pc} v ^{-1/2} mA V ^{-1/2} s ^{1/2}	I _{pa} /I _{pc}	-E _{pc} V vs. SCE	I _{pc} v ^{-1/2} mA V ^{-1/2} s ^{1/2}	I _{pc2} /I _{pc1}
I	0.05	0.95	0.056	0.97	1.69	0.097	1.92
	0.50	0.97	0.053	1.00	1.75	0.086	1.74
II	0.05	1.03	0.047	0.95	1.89	0.069	1.54
	0.50	1.04	0.043	1.00	1.97	0.066	1.50

generator (PARC model 175) and an X-Y recorder (PARC model RE 0091). For rapid scan rates a microcomputer (IBM-PC/XT) equipped with the proper software was used¹³. The controlled potential electrolysis experiments were performed using a potentiostat/galvanostat (PARC model 173) and a digital coulometer (PARC model 179).

For cyclic voltammetry, the cell was a three electrode, two compartment design. The working electrode was a glassy carbon disc (Tokai Carbon Co. Type CG30) of 0.07 cm² area, sealed into glass and polished between experiments. The counter electrode was a Pt ring below the working electrode and the reference was a SCE (Metrohm model EA 402) that was placed within a Luggin probe. The controlled potential electrolyses were carried out using a three compartment cell, with a 4 cm² glassy carbon plate and 4 cm² Pt gauze acting as cathode and anode, respectively. The catholyte and anolyte were separated by a fine glass sinter.

Analysis of the products was performed in a gas chromatograph (model CG-37002) with a FID detector. A 1.2 m x 4 mm column packed with Carbowax 20 M/2% KOH operated at 110 °C and nitrogen as the carrier. The product yields were estimated by comparison of the peak areas with those of standards.

Results and Discussion

Cyclic voltammetry

The cyclic voltammetric behaviour was investigated for aliphatic amines protected by the 4- or 3-nitrobenzoyl group in DMF/Bu₄NBF₄ 0.1 mol dm⁻³.

The isomers N-N-butyl-4-nitrobenzamide (I) and N-N-butyl-3-nitrobenzamide (II) present two reduction peaks in the range of potentials studied (Fig. 1). The influence of the scan rate on the cyclic voltammetric parameters is summarized in Table 1.

The first cathodic peak (1c) resembles a reversible one electron process, presenting on the anodic sweep a peak (1a) corresponding to the reoxidation of the N-N-butyl 4- or 3-nitrobenzamide anion radicals. The current function for this cathodic peak decreases slightly as the scan rate increases and the ratio of the anodic peak current to the cathodic peak current increases reaching unity when the

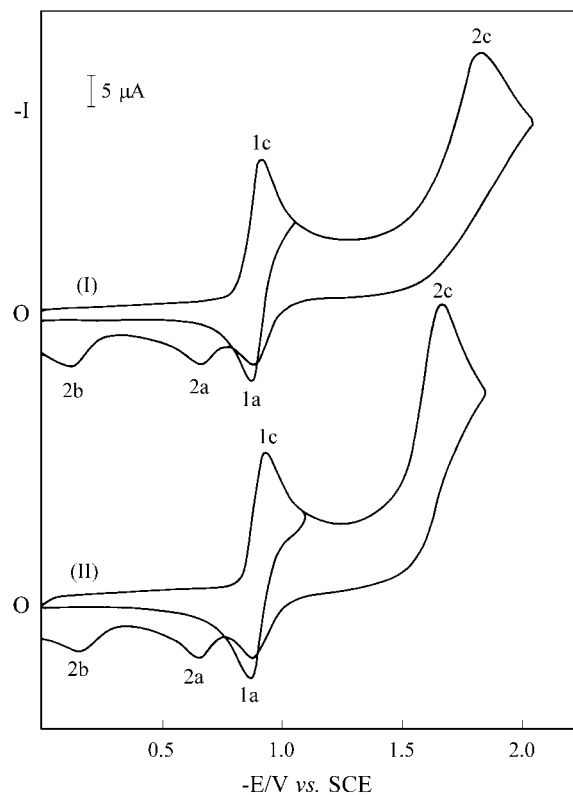


Figure 1. Cyclic voltammograms for 1 mmol dm⁻³ nitrobenzamides in DMF/Bu₄NBF₄ (0.1 mol dm⁻³) at a glassy carbon electrode. (I) N-N-butyl-3-nitrobenzamide and (II) N-N-butyl-4-nitrobenzamide. v = 0.10 V s⁻¹, 25 °C.

scan rate increases. This behaviour may be indicative that the product of the electron transfer reaction is being consumed by a very slow chemical reaction (EC process).

The second reduction step can be seen at potentials between -1.5 and -2.0 V vs. SCE. In the anodic sweep two peaks can be observed at potentials around -0.7 V (2a) and -0.1 V (2b) resulting from the reoxidation of some electroactive material generated in the second cathodic step. A comparison of the two cathodic peak heights (Table 1) shows that, for the isomer I, the cathodic peak current for the second step is approximately the double of the first at low scan rates, suggesting that the second reduction process seems to involve 2e⁻. Moreover, a decrease on the current

function and of the magnitude of the second peak is observed with increasing scan rate. Although this decrease is minor in compound II, the behaviour for this second step resembles an ECE process. On a slightly longer timescale, the dianion formed by reduction of the anion radical undergoes a chemical reaction, whose product is reduced again at the same potential. At low temperature ($-65\text{ }^{\circ}\text{C}$) a similar behaviour is observed, indicating that the electroactive product deriving from the chemical reaction decreases, leading to a decay of the second cathodic peak height. Furthermore, the suppression of the anodic peaks 2a and 2b is observed (Fig. 2).

The cyclic voltammograms for compounds I and II with subsequent sweeps at concentrations of about 10 mmol dm^{-3} , when the potential is limited after first peak show a

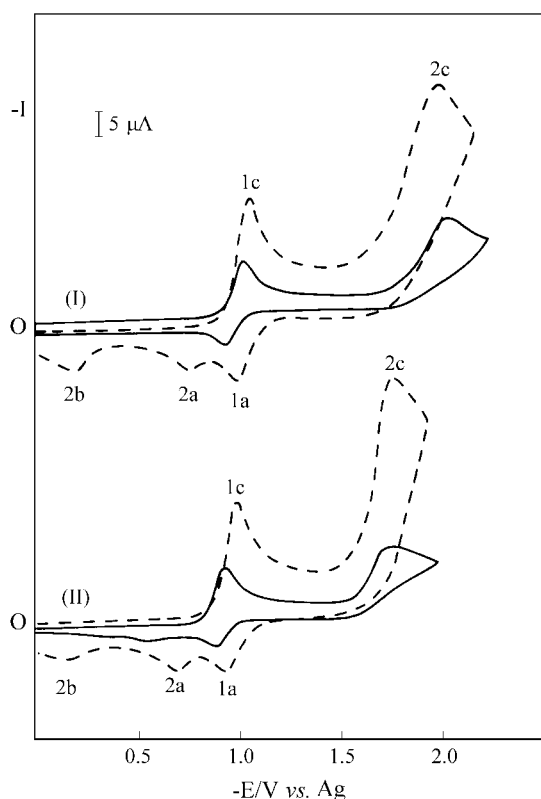


Figure 2. Cyclic voltammograms for 1 mmol dm^{-3} nitrobenzamides in $\text{DMF/Bu}_4\text{NBF}_4$ (0.1 mol dm^{-3}) recorded at 0.10 V s^{-1} . ---- $25\text{ }^{\circ}\text{C}$; — $-65\text{ }^{\circ}\text{C}$. Reference potential not adjusted to work temperature. (I) N-N-butyl-3-nitrobenzamide and (II) N-N-butyl-4-nitrobenzamide.

decrease of the current of this peak due to diffusion. However, when repetitive cycles, comprising the two first peaks are recorded, the current of the first peak, in the second cycle, diminishes by about 60 and 70% for the isomers I and II, respectively. Additionally, the appearance of a new cathodic reversible peak (3c) can be observed around -1.2 V . This peak probably results from a reaction of some species generated after the reduction of the anion radical with the starting material.

Controlled-potential electrolysis

All reductions were carried out on 10 mmol dm^{-3} solutions of nitrobenzamides in $\text{DMF/Bu}_4\text{NBF}_4$ 0.1 mol dm^{-3} . For the two isomers, the $\log I-t$ curves show a curvature and the n -values obtained are nonintegral, indicating the effect of the coupled chemical reactions to the electrodic process. Quantitative results and the respective electrolysis potentials are summarized in Table 2. An analysis of these results, shows that one electron is transferred to the isomers I and II at the first reduction potential while two are transferred at the second reduction potential.

At the end of the electrolyses, the catholytes were examined by cyclic voltammetry, and the n -butylamine produced as a result of the CN bond cleavage, was examined by gas-liquid chromatography (GLC). When the electrolyses of these compounds were carried out at the potential corresponding to the first cathodic peak, the n -butylamine was detected with yields of *ca.* 26 and 11% for I and II, respectively, indicating that, although the CN cleavage occurs, it is a secondary process. The cyclic voltammograms of the catholytes, after electrolysis, show a consumption of the starting material and present two cathodic peaks. One reversible process can be seen at about -1.2 V . The other peak is coincident with the second cathodic peak (2c), which was verified before the electrolysis (Fig.3).

When the electrolysis was carried out at potentials of the second peak, the yield of N -butylamine was *ca.* 52 and 70% for I and II respectively, suggesting that the compounds studied involve predominant scission of the CN bond. Furthermore, a similar cyclic voltammogram was found to that observed when the electrolysis was carried out at potentials of the first peak. This indicates that the same product is generated when the electrolysis is performed at

Table 2. Controlled potential electrolysis of 10 mmol dm^{-3} nitrobenzamides in $\text{DMF/Bu}_4\text{NBF}_4$ (0.1 mol dm^{-3}). Glassy carbon cathode.

Compound	$-E/V$ (vs. SCE)	n -value	yield of N -butylamine/%
I	1.25	1.02 ± 0.05	26
	2.07	2.94 ± 0.04	52
II	1.30	1.03 ± 0.06	11
	2.20	2.71 ± 0.06	70

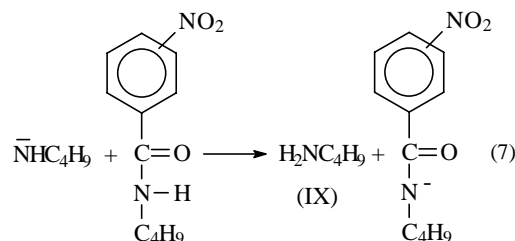
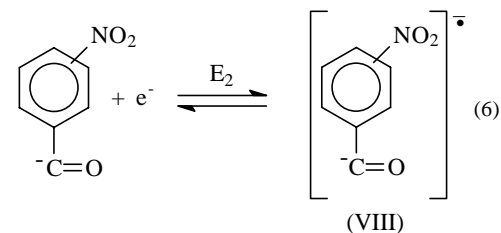
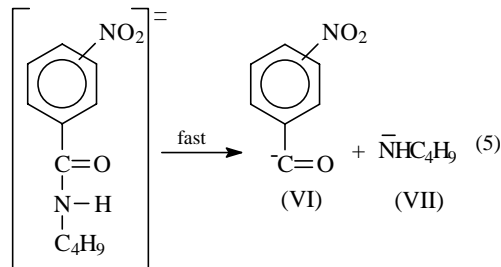
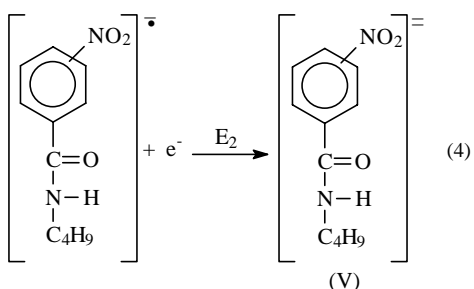
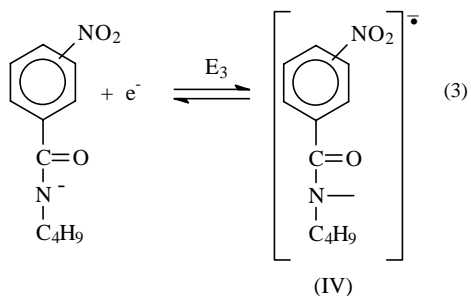
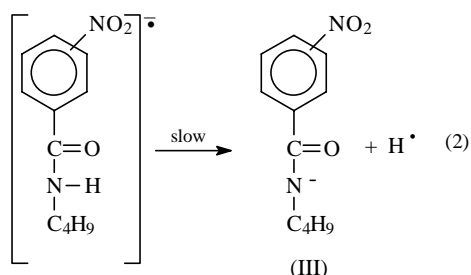
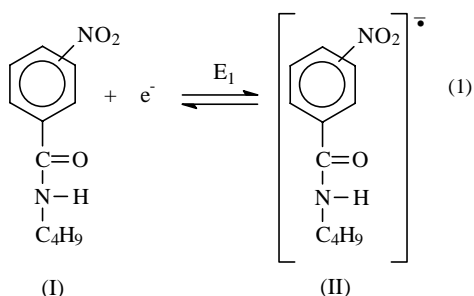
potentials of the first or second peak of the investigated compounds.

The obtained results suggest that the studied benzamides are reduced through mechanism represented by reactions 1-7 below.

Accordingly, the nitrobenzamides are first reduced by a one electron cathodic process (Eq. 1), to the corresponding anion radicals. These anion radicals are rather stable, considering that they present a peak (1a) corresponding to its reoxidation as shown in Fig. 1. However, secondary benzamides have acidic properties and the proton transfer

is coupled with the electrode reactions. In that case, it is probable that the species (II) decomposes, according to the stoichiometry stated by Eq. (2), yielding the corresponding nitrobenzamide anions, as it happens to the benzenesulfonamides nitrosubstituted^{4,14}. The anions (III) are reduced to the stable dianion radical (IV) in a chemically reversible, one-electron step (Eq. 3).

The second charge transfer step arises by the reduction of the anion radicals to their dianions, as may be observed in Eq. 4. As evidenced by the absence of a corresponding anodic peak at all scan rates studied, the dianions (V) decompose rapidly to give the corresponding nitrobenzoyl anion (VI) and the anion VII (Eq. 5). The species (VI) are electroactive at the potential of the second cathodic peak, explaining the coulometric results (Table 2) that show that this step involves the transfer of two electrons. When the temperature is lowered to $-65\text{ }^{\circ}\text{C}$, the chemical reaction is thermally quenched as indicated by a marked decrease in the height of the peak 2c regarding that observed at room temperature. Under these conditions the disappearance of the anodic peak 2a is also observed, which probably results from the reoxidation of the dianion radical VIII.



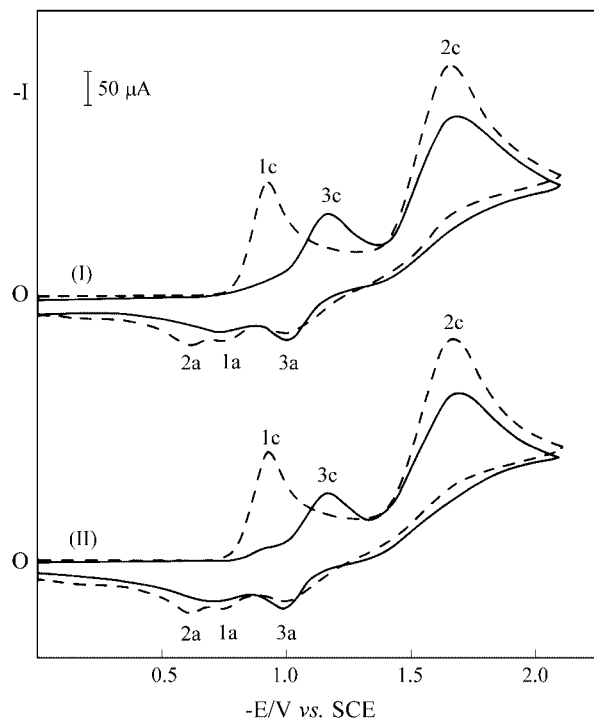


Figure 3. Cyclic voltammograms of N-N-butyl-4-nitrobenzamide 10 mmol dm^{-3} . (---) before, (—) after electrolysis. Potential scan rate 0.10 V s^{-1} . (I) -1.25 V vs. SCE ; (II) -2.07 V vs. SCE .

more, it is reasonable to assume that the anion VII is protonated by the nitrobenzamide giving the free amine detected by GLC with good yields (Table 2). This reaction is responsible for the depletion of starting material from the electrode surface at the second successive sweep as can be seen in Fig. 2.

The electrochemical behaviour of the N-N-butyl-4- and 3-nitrobenzamides established that cathodic cleavage of the nitrobenzoyl group in aprotic medium occurs at potentials between -1.5 and -2.0 V vs. SCE , showing that the removal of this group is electrochemically feasible.

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