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ELECTROCHEMICAL BEHAVIOUR OF BENZIMIDAZOLES II. PREPARATION OF A BIOLOGICALLY ACTIVE COMPOUND BY ELECTROREDUCTIVE DECARBOXYMETHYLATION

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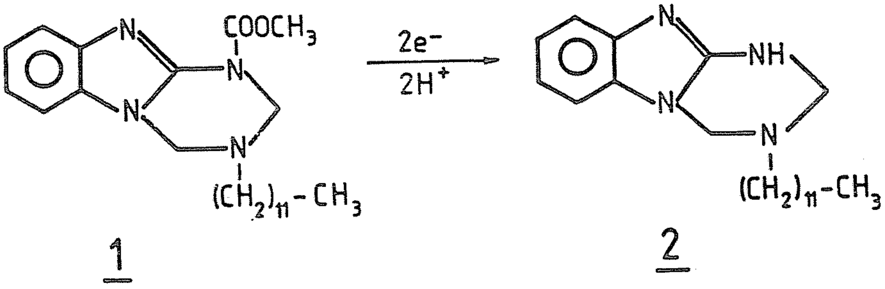
Abstract

Based on steady-state voltammetric experiments, preparative electrochemical reduction of the 1,3,5-triazino-(1,2-a)-benzimidazole-1(2H)-carboxylic acid-3-dodecyl-3,4-dihydro-, methylester **1** was carried out on Hg, Pb and Pt cathodes, in DMF/TBAP and MeCN/TBAP electrolytes. In all cases reduction resulted in the decarboxymethylated derivative **2** by cleavage of the carbon–nitrogen bond. The best product and current yield for **2** formation could be achieved when Pt was used as cathode material, MeCN/TBAP as electrolyte, a divided cell and constant current density in the range 15–25 mA/cm^2, or working at constant potential between 1.6 and 2.3 V vs Ag/AgI electrode. The reaction mechanism seemed to that of the activated halides.

Keywords: electrochemical reduction, electroreductive decarboxymethylation.

Introduction

As part of a broad programme concerning the examination of the electrochemical behaviour of benzimidazoles, the cathodic reduction of 1,3,5-triazino-(1,2-a) benzimidazole-1(2H)-carboxylic acid-3-dodecyl-3,4-dihydro-, methylester **1** was investigated in non-aqueous media.



Only a small number of papers have been published on the electrochemical reduction of benzimidazoles in spite of the importance of these compounds in polymer chemistry and in biological systems. In most cases only sidechain reduction occurred both in aqueous and non-aqueous solutions, and the benzimidazole ring remained untouched [1-5].

It was anticipated by us that by the electrochemical reduction of **1** in non-aqueous systems either an elimination reaction or a coupling reaction – to form dimeric species – would occur.

In this paper the electrochemical reduction of **1** on various cathode materials in non-aqueous electrolytes is described with the aim either to clarify the product(s) and the reaction pathway, or to identify the optimum conditions for a useful product formation.

Experimental

The synthesis of the starting material **1** was carried out by a method described by CHAVANNES et al. [6]. DMF and acetonitrile (MeCN) were purified and dried as previously reported [7,8]. Tetrabutylammonium perchlorate (TBAP) and tetrabutylammonium ioide (TBAI) – both Fluka products – were used as supporting electrolytes.

The electrochemical instrumentation – including the electrolysis cell assembly – employed in voltammetry and preparative electrolyses – has been described in our earlier paper [9]. The cathode was made of the metal under study, the anode was always a Pt sheet. All potentials were referred to a Ag/AgI reference electrode, where TBAI was used as supporting electrolyte. All measurements were performed at room temperature.

The electrolyses were followed up by thin layer chromatography (t.l.c.) on Kieselgel $60_{F_{254}}$ (Merck) plates with 0.25 mm thickness of the layer using $CHCl_3$:CCl_4:CH_3OH=8:5:1 as eluent, and the spots detected under UV light. R_f values: 0.41 for **1** and 0.33 for the reduction product.

Typical preparative scale experiments were carried out either at constant current density or potentiostatically. The catholyte consisted of the starting material ($1.25 \cdot 10^{-2}$mol/l) dissolved in DMF or MeCN containing 0.1 mol/l TBAP, the anolyte was the supporting electrolyte itself.

After electrolysis the electrolyte was poured onto water and the cream-coloured precipitate **2** was formed. It was filtered off, washed with water and dried in vacuo. The structure of **2** was determined by spectroscopic methods.

The UV spectrum was recorded on a Unicam SP-200 spectrophotometer, and the IR spectrum on a Zeiss UR-20 spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded at 80 and 20.1 MHz, respectively, on a Bruker WP-80

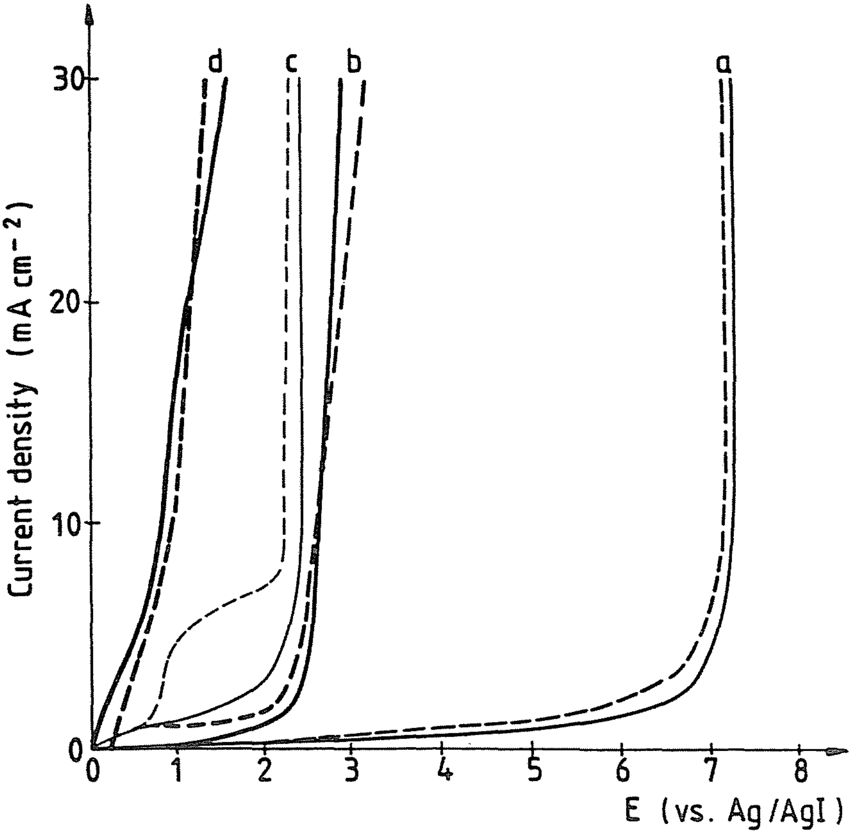


Fig. 1. Steady-state polarization curves for the reduction of 1,3,5-triazino-(1,2-a) benzimidazole-1(2H)-carboxylic acid-, -3-dodecyl-3,4-dihydro-, methylester in DMF/TBAP (0.1 mol/l) electrolyte at different cathodes; (—) without the starting material; (- - -) with $1.25 \cdot 10^{-2}$ mol/l starting material. a) Hg; b)Pt; c)Pb; d) graphite.

spectrometer. Tetramethylsilane was used as internal reference (TMS=0.00 ppm) in the NMR spectra.

The characteristics of **2** are as follows: UV (in 96% ethanol) λ_{max}(nm) (lg ϵ): 286 (3.96); 249 (3.88); 212 (4.30). IR (KBr) (cm^{-1}): 2700–3350 NH; 1650 C=N. ^{1}H NMR (in DMSO-d$_6$) δ (ppm): 6.75-7.30 m (4H) 6,7,8,9-H; 4.99 s (2H) 4-H$_2$; 4.24 s (2H); 2-H$_2$; 2.5 in overlap N(3)-CH$_2$; 1.25 s (20H) (CH$_2$)$_{10}$; 0.85 t (3H) CH$_3$. ^{13}C NMR (in DMSO-d$_6$)δ (ppm): 151.5 C (10a); 142.2 C(9a); 133.2 C(5a); 120.4 C(7); 117.9 C(8); 114.9 C(9); 107.1 C(6); 62.6 C(4); 59.7 C(2); 49.5 N(3)-CH$_2$; 31.2-22.0 (CH$_2$)$_{10}$; 13.8 CH$_3$.

Results and Discussion

Figs. 1 and *2* show steady-state polarization curves for the reduction of **1** at Hg, Pb, Pt and graphite cathodes in DMF/TBAP and MeCN/TBAP electrolytes, respectively; for comparison, the polarization curves of the supporting electrolytes are also given.

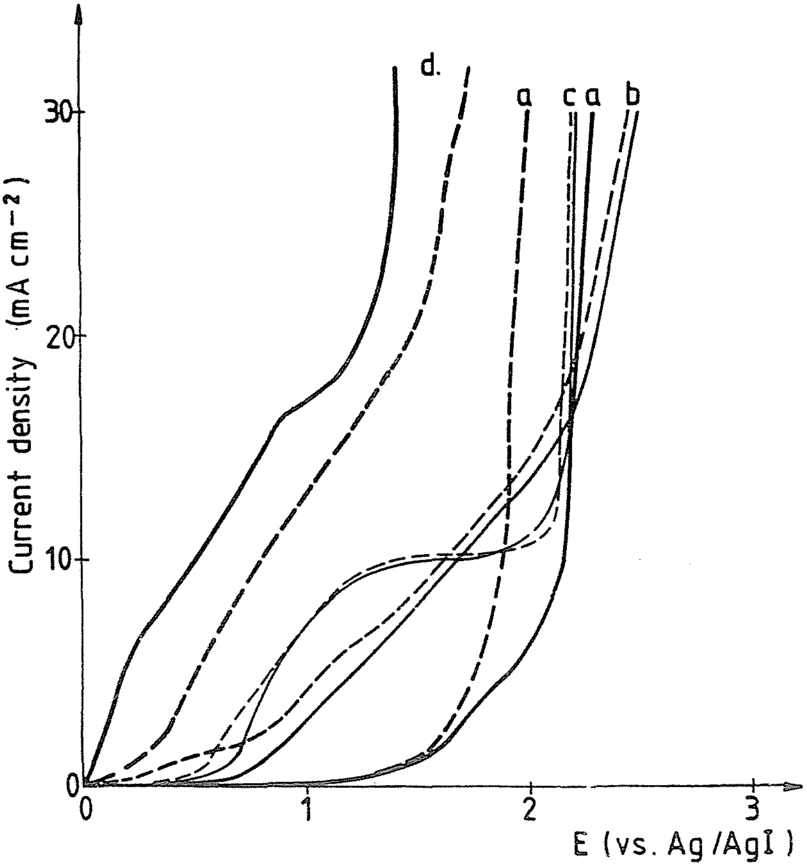


Fig. 2. Steady-state polarization curves for the reduction of 1,3,5-triazino-(1,2-a) benzimidazole-1(2H)-carboxylic acid-, -3-dodecyl-3,4-dihydro-, methylester in MeCN/TBAP (0.1 mol/l) electrolyte at different cathodes; (—) without the starting material; (- - -) with $1.25 \cdot 10^{-2}$ mol/l starting material. a) Hg; b)Pt; c)Pb; d) graphite.

It can be seen that a graphite electrode is unsuitable for the reduction of **1**, since hydrogen evolution starts at very low potentials in both non-aqueous electrolytes. Using DMF as solvent and Hg, Pb and Pt as cathodes, no current increase was observed prior to hydrogen evolution. Addition of **1** did not alter considerably the basic $i - E$ curves recorded on Pt and Hg cathodes, while at a Pb cathode the $i - E$ profile was changed, indicating reduction of **1** at potentials much lower than those needed for hydrogen evolution (*Fig. 1*). The polarization curves in MeCN/TBAP electrolytes (*Fig. 2*) show that the reduction of **1** can be effected on Hg, Pb and Pt electrodes before the onset of hydrogen evolution, however, on lead, because of the low ($< 5\text{mA/cm}^2$) current density, the reduction would be too slow for preparative purposes. The low current densities in most cases can be attributed to the poor conductivity of the non-aqueous electrolytes used.

Taking the above experiments into account, a series of constant-current as well as potentiostatic electrolyses was carried out on Hg, Pb and Pt electrodes in DMF/TBAP and on Hg and Pt electrodes in MeCN/TBAP electrolytes.

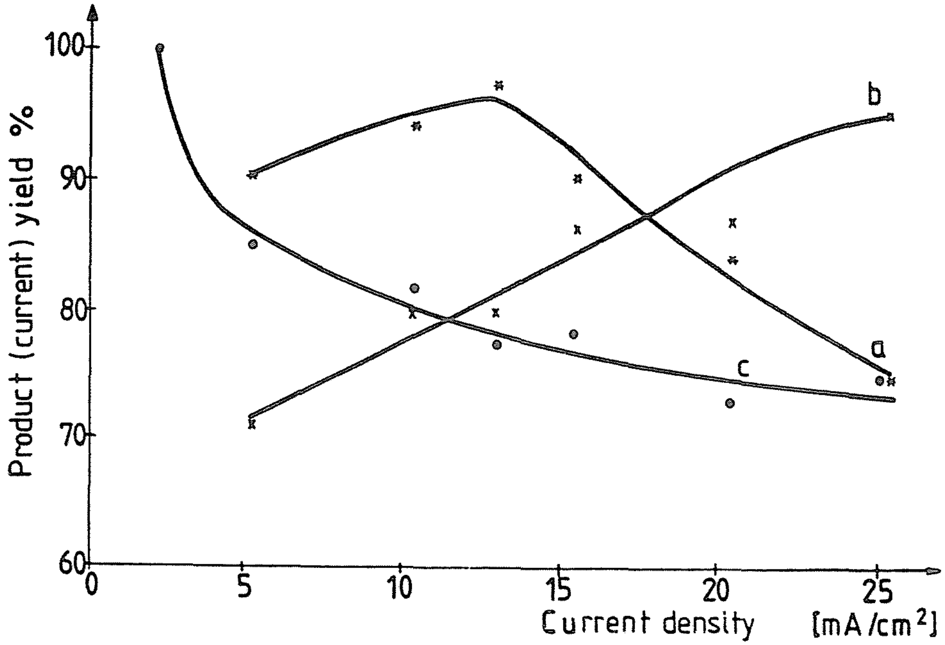


Fig. 3. Dependence of product (current) yield on the current density for the reduction of 1,3,5-triazino-(1,2-a) benzimidazole-1(2H)-carboxylic acid-, -3-dodecyl-3,4-dihydro-, methylester in DMF/TBAP (0.1 mol/l) electrolyte at different cathodes; Starting material concentration: $1.25 \cdot 10^{-2}$ mol/l; a) Hg; b)Pt; c)Pb.

Preparative electrochemical reduction of **1**, in accordance with our expectations, gave only one product (**2**) in all cases. The structure of the reduction product **2**, which proved to be a compound with considerable fungicidal activity, was the decarboxymethylated derivative of **1** : 3-dodecyl-3,4-dihydro-1,3,5-triazino-(1,2-a)-benzimidazole (scheme see below).

The results of our preparative studies are summarized in *Tables 1–3*. In each experiment the amount of electricity consumed was exactly 2 F/mol, and the starting material concentration $1.25 \cdot 10^{-2}$ mol/l. The product (and current) yield vs current density plots are in *Figs. 3* and *4*.

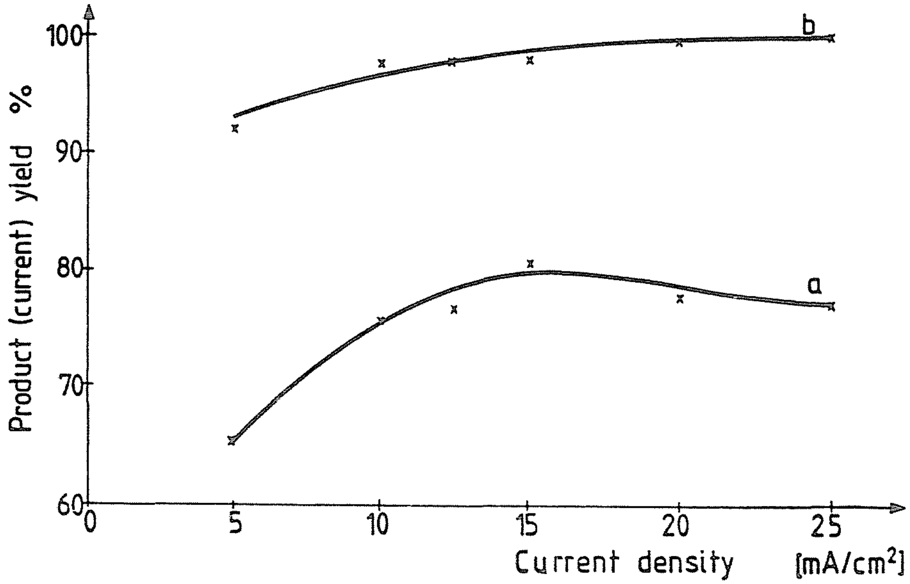


Fig. 4. Dependence of product (current) yield on the current density for the reduction of 1,3,5-triazino-(1,2-a) benzimidazole-1(2H)-carboxylic acid-, -3-dodecyl-3,4-dihydro-, methyl-ester in MeCN/TBAP (0.1 mol/l) electrolyte at a) Hg; b)Pb cathodes. Starting material concentration: $1.25 \cdot 10^{-2}$ mol/l;

The above data clearly show that the electrochemical reductive cleavage of the carboxymethyl group of **1** can be performed on Hg, Pb and Pt cathodes in DMF/TBAP and on Hg and Pt cathodes in MeCN/TBAP electrolytes either galvanostatically or potentiostatically, with no other byproduct than hydrogen. However, the most advantageous electroreduction process was achieved when using Pt as cathode material and MeCN/TBAP

Table 1
Electrochemical reduction of 1,3,5-triazino(1,2-a)benzimidazole-1(2H)-carboxylic acid-, -3-dodecyl-3,4-dihydro-, methylester in DMF/TBAP (0.1 mol/l) electrolyte [a]

Electrode	Current density (mA/cm^2)	Potential (V vs. Ag/AgI)	Cell voltage (V)	Product (current) yield[b] (%)
Hg	5	1.65–2.50	12–20	90.5
	10	2.0–2.63	19–31	94.0
	12.5	2.3–2.70	42–55	97.5
	15	2.54–2.93	53–69	90.0
	20	2.63–3.03	67–89	84.5
	25	2.73–3.25	88–96	75.0
Pt	5	1.90–2.25	17–18	71.0
	10	2.0–2.26	25–26	80.0
	12.5	2.10–2.30	28–30	80.0
	15	2.20–2.30	38–42	86.5
	20	2.26–2.38	50–55	87.0
	25	2.28–2.46	60–67	95.5
Pb	2	0.80–1.50	6–8	100.0
	5	1.13–2.20	8–10	95.0
	10	1.55–2.30	15–17	82.0
	12.5	1.75–2.30	20–25	77.5
	15	1.90–2.33	29–39	78.5
	20	2.33–2.39	40–44	73.0
	25	2.40–2.51	42–46	75.0

[a] Electrolysis terminated after 2.0 F mol^{-1} of starting material; starting material concentration: $1.25 \cdot 10^{-2}$ mol/l;

[b] Product yields were determined gravimetrically. The purity of the product was checked by HPLC

as electrolyte and a current density of about 25 mA/cm^2, since the conversion, the product and current yield did not decrease even at higher current densities and the cell voltage was relatively low. Increasing the amount of electricity consumed over 2 F/mol resulted in decreasing current efficiencies, but the product yield remained the same as before.

The reduction of **1** to **2** proceeded with an overall transfer of two electrons per molecule. The reaction mechanism was not elucidated in detail, however, it seemed to be similar to that proposed for the reduction of activated halides. The reductive cleavage occurs by a concerted electron-transfer bond-breaking process to produce the resultant free radical at the electrode surface, followed by a fast reduction to the carbanion and hydrogen abstraction from the electrolyte [10–13].

Table 2
Electrochemical reduction of 1,3,5-triazino(1,2-a)benzimidazole-1(2H)-carboxylic acid-, -3-dodecyl-3,4-dihydro-, methylester in MeCN/TBAP (0.1 mol/l) electrolyte [a]

Electrode	Current density (mA/cm^2)	Potential (V vs. Ag/AgI)	Cell voltage (V)	Product (current) yield[b] (%)
Hg	5	1.90–2.25	17–18	65.5
	10	2.29–2.41	25–26	76.0
	12.5	2.20–2.26	29–30	77.0
	15	2.26–2.30	40–42	81.0
	20	2.30–2.50	46–48	78.0
	25	2.36–2.63	50–54	77.5
Pt	5	1.30–1.50	16–18	92.0
	10	1.50 –1.90	19–22	97.5
	12.5	1.80–2.22	23–27	98.0
	15	1.92–2.30	30–39	98.0
	20	1.95–2.34	36–40	99.5
	25	2.05–2.46	42–46	99.9

[a] Electrolysis terminated after 2.0 F mol^{-1} of starting material; starting material concentration: $1.25 \cdot 10^{-2}$ mol/l;

[b] Product yields were determined gravimetrically. The purity of the product was checked by HPLC.

Conclusion

The electrochemical reductive cleavage of the C-N bond in **1** can be effected with high conversion, product and current yield under the following electrolysis conditions:

(a) using a two-compartment cell
(b) using MeCN/TBAP as electrolyte
(c) using Pt as cathode
(d) working at constant current density in the range of 15–25 mA/cm^2 or potentiostatically between 1.6 and 2.3 V vs Ag/AgI electrode.

Table 3

Electrochemical reduction of 1,3,5-triazino(1,2-a)benzimidazole-1(2H)-carboxylic acid-, -3-dodecyl-3,4-dihydro-, methylester at different potentials [a]

Electrode	Electrolyte	Potential (V vs. Ag/AgI)	Current density (mA/cm^2)	Cell voltage (V)	Product (current) yield[b] (%)
Hg	DMF/TBAP	2.0	13–1.0	40–42	85.0
		2.2	20–3.0	50–60	92.0
		2.8	31–4.0	70–75	96.5
Pb	DMF/TBAP	1.5	21–3.0	5– 8	100.0
		2.0	47–5.0	10–20	76.7
		2.3	52–5.0	70–78	69.0
Pt	DMF/TBAP	2.0	24–4.0	42–43	98.2
		2.25	25–4.0	46–47	80.2
Pt	MeCN/TBAP	1.5	11–6.0	19–14	78.0
		2.0	25–5.0	42–43	100.0

[a] Electrolysis terminated after 2.0 F mol^{-1} of starting material;starting material concentration: 1.25 10^{-2} mol/l;

[b] Product yields were determined gravimetrically. The purity of the product was checked by HPLC

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