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ORIGINAL PAPER

Investigations on electrochemical α-methoxylation of selected dipeptides

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Abstract Voltamperometric studies on the indirect electrochemical α-methoxylation of Boc-Pro-Gly-OMe and Boc-Val-Gly-OMe in MeOH in the presence of NaCl or NaBr as the mediator suggested that the first reaction step was a direct *N*-halogenation of the dipeptide by active chlorine or bromine adsorbed on the electrode surface. The kind of mediator (NaCl or NaBr), its concentration, the current density, and the applied electric charge had a significant influence on the reaction course. In the case of Boc-Pro-Gly-OMe, the use of sodium bromide was necessary to obtain a relatively high ratio of α-monomethoxylation to α,α-dimethoxylation. For Boc-Val-Gly-OMe, the selectivity for α-monomethoxylation was close to 100%, independently of the mediator. Optimisation of the selected electrolysis parameters allowed us to significantly improve the yield and selectivity of the α-methoxylation of Boc-Pro-Gly-OMe (Kardassis et al. Tetrahedron 54:3471, 1998) and to obtain good results in the α-methoxylation of Boc-Val-Gly-OMe.

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1 Introduction

Both natural non-proteinogenic amino acids and unnatural synthetic amino acids are interesting bioactive compounds. Many of them are used as active pharmaceutical ingredients or building blocks for peptide pharmaceuticals or other large therapeutic structures. The number of peptide pharmaceuticals is growing very fast; currently, they comprise a considerable part of the drug market [1, 2]. Both types of amino acids are available on a larger scale only by synthesis. Because of this, the development of enantioselective methods for the preparation of α-amino acids has attracted significant attention from organic chemists. Electrochemical anodic α-alkoxylation is one of the most promising methods for functionalisation of the α position of α-amino acid derivatives and simple peptides [3–6].

In recent studies, we tried to develop a method for the enantioselective synthesis of α-amino acids starting from chiral 3-triphenylphosphine-2,5-piperazinediones **3a-b** [7]. A key step in the synthesis of these compounds was electrochemical α-methoxylation of the glycine moiety in the protected dipeptides Boc-Pro-Gly-OMe (**1a**) or Boc-Val-Gly-OMe (**1b**) (Fig. 1).

Because of the multistage nature of these syntheses, high yields and selectivities in the α-methoxylation were desirable. Electrochemical α-methoxylation of *N*-protected α-amino acid esters or dipeptides, including cyclic dipeptides (2,5-piperazinediones), has been previously investigated by electrochemists [3, 8–11]. The direct electrochemical α-methoxylation of these compounds was unsuccessful [9]. Conversely, indirect α-methoxylation

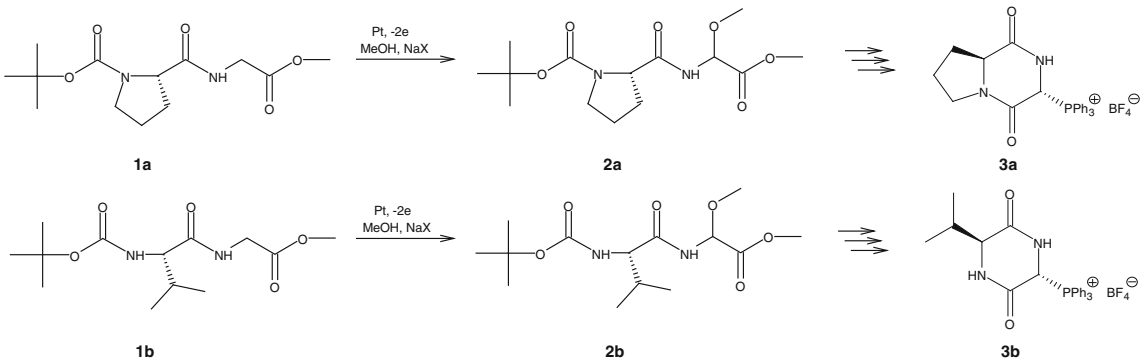

Fig. 1 Synthesis of 3-triphenylphosphonie-2,5-piperazinediones **3a-b**

with NaCl or NaBr as an *N*-halogenating agent gives the expected α-methoxylation products. According to the literature, there are three main issues to overcome in the α-monomethoxylation of the glycine moiety of *N*-acylated dipeptide esters with glycine as the *C*-terminal amino acid: (i) regioselectivity of methoxylation at the *C*-terminus versus the *N*-terminus, (ii) selectivity for α-monomethoxylation of the glycine residue versus α,α-dimethoxylation and (iii) satisfactory turnover of the starting dipeptide [9]. The results of our preliminary investigations on the electrochemical methoxylation of selected dipeptides based on literature studies [8, 10] were not satisfying. In this report, we tried to find optimal conditions for these reactions. To gain better insight into the mechanism of α-methoxylation, we also carried out voltamperometric investigations of this transformation.

2 Materials and methods

Analytical grade reagents manufactured by POCh S.A. Gliwice, Poland, were used. Structures of the obtained products were determined by ^{1}H-NMR (Varian NMR Unity-Inova 300 MHz) and compared with literature data [8, 10]. According to literature suggestions [8, 10], both the voltammetric investigations and preparative experiments were carried out in methanol solution in the presence of NaCl or NaBr as *N*-halogenating agents and $LiClO_4$ as a supporting electrolyte.

2.1 Voltammetric investigations

The main part of the apparatus for the voltammetric investigations was a two-chamber electrolyzer with a test electrode (Pt-1 cm^2), auxiliary platinum electrode, and Haber-Lugin capillary with a Ag/AgCl (in 5% LiCl in anhydrous methanol) as reference electrode placed inside. The electrolyzer was powered through a potentiostat (AUTOLAB PGSTAT 30) operated by General Purpose Electrochemical System (GPES) software. The tests were carried out at 20 °C over a potential range of 0.5–2.5 V versus Ag/AgCl at a rate of potential scanning of 200 mV s^{-1}.

The following solutions were examined:

- methanol + $LiClO_4$ (0.1 mol L^{-1}),
- methanol + $LiClO_4$ (0.1 mol L^{-1}) + NaBr (0.017 mol L^{-1}),
- methanol + $LiClO_4$ (0.1 mol L^{-1}) + NaBr (0.017 mol L^{-1}) + Boc-Pro-Gly-OMe (**1a**) (0.017 mol L^{-1}),
- methanol + $LiClO_4$ (0.1 mol L^{-1}) + NaCl (0.017 mol L^{-1}),
- methanol + $LiClO_4$ (0.1 mol L^{-1}) + NaCl (0.017 mol L^{-1}) + Boc-Pro-Gly-OMe (**1a**) (0.017 mol L^{-1}).

2.2 Electrochemical methoxylation of dipeptides **1a** and **1b**

The electrochemical methoxylation of Boc-Pro-Gly-OMe (**1a**) and Boc-Val-Gly-OMe (**1b**) was carried out in an undivided electrolyzer (50 cm^3 vol.). The anode was made of platinum foil (11 cm^2), and the cathode was made of platinised titanium. The electrolyzer power source was an UNITRA ZT-980-4. The dipeptide (DIP) **1a** (0.075 g, 0.262 mmol) or **1b** (0.075 g, 0.260 mmol) and the sodium halide (S) were dissolved in 1 M $LiClO_4$ in methanol (15 cm^3) and electrolyzed. The applied electric charge was equal to 2 F mol^{-1} of dipeptide. Caution was exercised when handling solutions containing $LiClO_4$; according to the literature recommendations [8–10], the methanol was evaporated in vacuo at room temperature. The resulting white residue was dissolved in water (20 cm^3) and extracted with four portions of CH_2Cl_2 (10 cm^3). The organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue, containing methoxylated dipeptides **2a-b,** was dissolved in $CDCl_3$ and analysed by NMR.

The schedule of the experiments on the electrochemical methoxylation of Boc-Pro-Gly-OMe (**1a**) and Boc-Val-

Gly-OMe (**1b**) are gathered in Table 1. In the case of experiment no. 19, the methoxylation was worked-up after 48 h. In experiment no. 20, the dipeptide was added after electrolysis and the reaction mixture was stirred for 15 min.

2.3 Calculations

The compositions of the organic residues obtained following work-up of the electrolytes were calculated based on ^{1}H-NMR spectra by comparing the integrals of the α-methine protons of the monomethoxylated dipeptides and the protons of the α,α-dimethoxy groups of the dimethoxylated dipeptides with the combined integrals of all of the *t*-butyl group signals, which were considered as an internal standard. Based on these results, the yields of the monomethoxy derivatives and the selectivity for monomethoxylation were calculated.

2.4 Synthesis of dipeptides **1a** and **1b**

The synthesis of *N*-tert-butoxycarbonyl-*L*-prolyl-glycine methyl ester **(1a)** was carried out using the Kardassis procedure [8]. *N*-tert-Butoxycarbonyl-L-valyl-glycine methyl ester **(1b)** was synthesised using the DCC method with the addition of hydroxybenzotriazole [12, 13]. The spectroscopic properties of the obtained products were compared with literature data [8, 12].

^{1}H-NMR data for the obtained methoxylated dipeptides:

N-tert-butoxycarbonyl-L-prolyl-D,L-α-methoxyglycine methyl ester (**2a**)

^{1}H-NMR: (both diastereoisomers $CDCl_3$) δ: 1.47 (9H, s, $C(CH_3)_3$), 3.42 (3H, s, OCH_3), 3.44–3.47 (2H, m, CH_2), 3.81 (3H, s, $COOCH_3$), 4.58–4.61 (1H, m, CH), 5.54 (1H, d, $J = 9.6$ Hz, $CHOCH_3$), 5.55 (1H, d, $J = 9.6$ Hz,

Table 1 The schedule of experiments on methoxylation of dipeptides

Entry	DIP	S	c_{DIP} (mol L^{-1})	c_S (mol L^{-1})	Molar ratio DIP:S	j (A dm^{-2})	τ (min)	t (°C)
1	**1a**	NaBr	0.017	0.017	1:1	0.2	31	20
2	**1a**	NaBr	0.017	0.017	1:1	0.5	12	20
3	**1a**	NaBr	0.017	0.017	1:1	1.0	6.3	20
4	**1a**	NaBr	0.017	0.017	1:1	1.5	4.2	20
5	**1a**	NaBr	0.017	0.017	1:1	2.0	3.3	20
6	**1a**	NaCl	0.017	0.017	1:1	0.2	31	20
7	**1a**	NaCl	0.017	0.017	1:1	0.5	12	20
8	**1a**	NaCl	0.017	0.017	1:1	1.0	6.3	20
9	**1a**	NaCl	0.017	0.017	1:1	1.5	4.2	20
10	**1a**	NaCl	0.017	0.017	1:1	2.0	3.3	20
11	**1a**	NaBr	0.017	0.00425	1:0.25	0.5	12	20
12	**1a**	NaBr	0.017	0.0085	1:0.5	0.5	12	20
13	**1a**	NaBr	0.017	0.034	1:2	0.5	12	20
14	**1a**	NaBr	0.017	0.068	1:4	0.5	12	20
15	**1a**	NaBr	0.017	0.017	1:1	0.5	12	−20
16	**1a**	NaBr	0.017	0.017	1:1	0.5	40	−20
17	**1a**	NaCl	0.017	0.017	1:1	0.5	12	−20
18	**1a**	NaCl	0.017	0.017	1:1	0.5	50	−20
19	**1a**	NaBr	0.017	0.017	1:1	0.5	12	20
20	**–**	NaBr	–	0.017	1:1	0.5	12	20
21	**1b**	NaBr	0.017	0.017	1:1	0.2	31	20
22	**1b**	NaBr	0.017	0.017	1:1	0.5	12	20
23	**1b**	NaBr	0.017	0.017	1:1	1.0	6.3	20
24	**1b**	NaBr	0.017	0.017	1:1	2.0	3.3	20
25	**1b**	NaCl	0.017	0.017	1:1	0.2	31	20
26	**1b**	NaCl	0.017	0.017	1:1	0.5	12	20
27	**1b**	NaCl	0.017	0.017	1:1	1.0	6.3	20
28	**1b**	NaCl	0.017	0.017	1:1	2.0	3.3	20
29	**1b**	NaCl	0.017	0.017	1:1	3.0	2.2	20
30	**1b**	NaCl	0.017	0.017	1:1	4.0	1.4	20

C**H**OCH$_3$), 7.08 (1H, broad, N**H**), 7.71 (1H, broad, N**H**) in accordance with literature data [8].

N-tert-butoxycarbonyl-L-valyl-D,L-α-methoxyglycine methyl ester (**2b**)

^{1}H-NMR: ^{1}H-NMR: (both diastereoisomers, $CDCl_3$) δ: 0.93 (3H, d, $J = 6.9$ Hz, C**H$_3$**), 0.94 (3H, d, $J = 6.9$ Hz, C**H$_3$**), 0.99 (3H, d, $J = 6.6$ Hz, C**H$_3$**), 1.01 (3H, d, $J = 6.6$ Hz, C**H$_3$**), 1.45 (2 × 9H, s, CH(C**H$_3$**)$_3$), 2.17–2.21 (2 × 1H, m, C**H**(CH$_3$)$_2$), 3.45 (2 × 3H, s, OC**H$_3$**), 3.81 (3H, s, COOC**H$_3$**), 4.18–4.21 (2 × 1H, m, C**H**), 5.09 (1H, t, $J = 8.4$ Hz N**H**), 5.56 (1H, d, $J = 9.4$ Hz, C**H**OCH$_3$), 5.57 (1H, d, $J = 9.0$ Hz, C**H**OCH$_3$), 7.14 (1H, broad, N**H**) in accordance with literature data [10].

3 Results and discussion

3.1 Voltammetric investigations

The voltamperometric curves for solutions of $LiClO_4$ and $LiClO_4$ + NaCl in MeOH are shown on Fig. 2. The chlorine release at the anode started at 1.25 V. The increase in current intensity was caused by the oxidation of chloride ions to atomic chlorine, which was adsorbed on the electrode surface. The adsorption process leads to blocking of the anode surface, resulting in a decrease of the chloride ion oxidation rate. As a consequence, in the range of 2.25–2.75 V, the current intensity of electrolysis with NaCl is lower than without it. The peak of reduction of the adsorbed chlorine to Cl^- anions was located on the returning curve at 0.75 V [14–19]. The addition of dipeptide **1a** to the $LiClO_4$ + NaCl methanol solution resulted in an increase in the current intensity (Fig. 3). Active chlorine adsorbed on the electrode surface reacts with dipeptide, which results in unblocking of the anode surface and further oxidation of chloride anions. Similar processes occur in analogous experiments with sodium bromide (Figs. 4 and 5). In these cases, bromine release started at 0.82 V. The increase in the current intensity caused by the oxidation of bromide anions to atomic bromine was clear in the voltamperometric curve at 1.35 V. The current intensity in the terminal part of the curve was higher than the current intensity observed in the solution free of bromide ions. Similar to chlorine, the adsorbed bromine blocks the electrode surface, however, in this case, the effect of this process on the oxidation rate decrease was much lower. The cathodic peak for the reduction of adsorbed bromine to bromide anions was present on the returning part of the curve at 0.58 V. The addition of dipeptide **1a** to a solution of $LiClO_4$ and NaBr in methanol resulted in a distinct increase of the current intensity (Fig. 5). Bromination of the dipeptide caused unblocking of the electrode surface and facilitated the oxidation of additional bromide anions. The anodic peak of the bromide anion oxidation was stronger and was shifted to 1.18 V. The cathodic peak was also stronger, and was shifted to about 0.8 V.

According to some literature data [3, 4, 9, 12], the first stage of the indirect α-methoxylation of *N*-acylamino acid esters in the presence of NaCl or NaBr as the mediator consists in formation of methyl hypochlorite or methyl hypobromite, followed by *N*-halogenation of the amide group with methyl hypohalite. The consecutive elimination of hydrogen halide and the addition of methanol to the active C=N bond leads to α-methoxylation of the glycine moiety (Fig. 6) [3, 4].

This hypothesis appears to be reasonable, as *t*-butyl hypochlorite in methanol is widely used for the *N*-chlorination of *N*-alkylamides [9]. The results of our voltamperometric studies, however, indicated that disappearance of chlorine or bromine from the anode surface is much more effective after the addition of dipeptide. This suggests that the dipeptide is *N*-halogenated directly by the active chlorine or bromine adsorbed on the electrode surface. The presence of the cathodic peaks of reduction of the absorbed halogen on the voltamperic curves even after addition of dipeptide can be explained assuming that the rate of halogen deposition on the anode surface is much higher then the rate of dipeptide *N*-halogenation. Our further investigations (see below) seem to confirm this assumption; the best yields of α-methoxylation of dipeptides were obtained at the applied charge 4.7–16.7 F per mol of a dipeptide and at relatively low current density.

3.2 Electrochemical methoxylation of dipeptides

The results of our investigations revealed that the course of α-methoxylation of the glycine moiety of dipeptides **1a** and

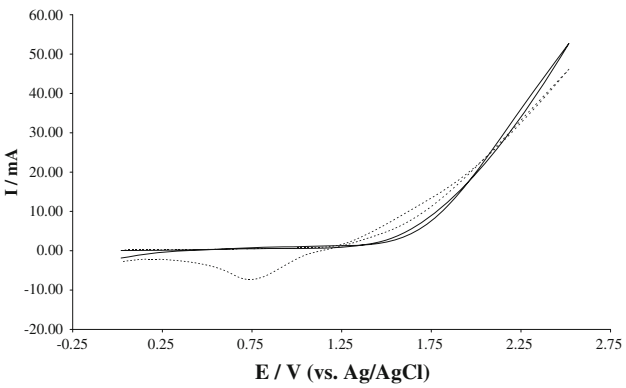

Fig. 2 Voltamperometric curves for methanol solution of $LiClO_4$ (*solid line*) and $LiClO_4$ + NaCl (*dotted line*)

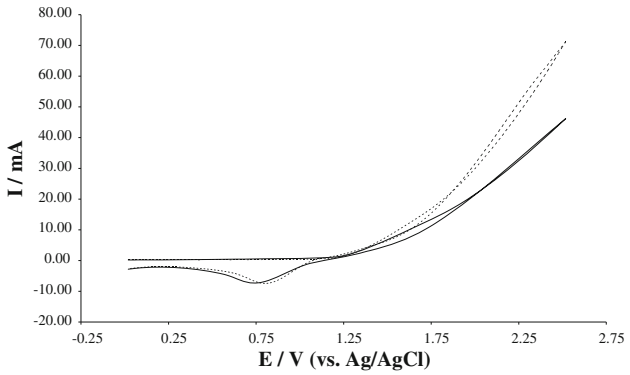

Fig. 3 Voltamperometric curves for methanol solution of $LiClO_4$ + NaCl (*solid line*) and $LiClO_4$ + NaCl + DIP **1a** (*dotted line*)

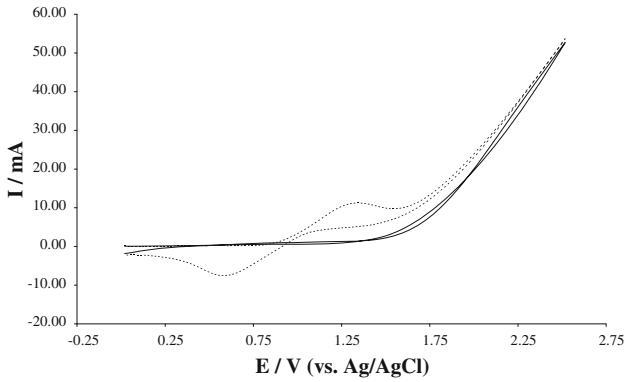

Fig. 4 Voltamperometric curves for methanol solution of $LiClO_4$ (*solid line*) and $LiClO_4$ + NaBr (*dotted line*)

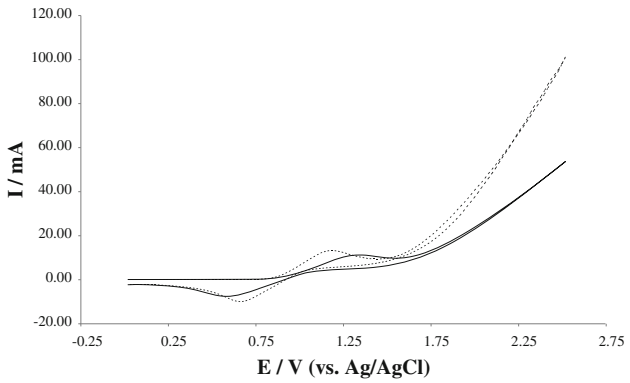

Fig. 5 Voltamperometric curves for methanol solution of $LiClO_4$ + NaBr (*solid line*) and $LiClO_4$ + NaBr + DIP **1a** (*dotted line*)

1b depends markedly on the variety of halogenating salt and the current density. In the case of dipeptide **1a,** in the range of about 0–0.5 A dm^{-2}, an increase in the current density resulted in an increase in monomethoxylation yield, independent of the salt used (Fig. 7). Above 0.5 A dm^{-2}, a decrease of the reaction yield was observed, probably because of the rising discrepancy between a rate of chlorine generation and a much lower rate of dipeptide *N*-chlorination. Above 0.7 A dm^{-2}, the reaction yield was higher in the case of sodium chloride compared to sodium bromide. Unfortunately, the selectivity for monomethoxylation in the presence of NaCl was lower. At a current density of 0.5 A dm^{-2}, about 6% of dipeptide **1a** was converted to the undesired dimethoxy derivative, whereas in the presence of sodium bromide, only a trace amount of dipeptide (<1%) was dimethoxylated.

As previously mentioned, we assume that the first stage of the electrochemical methoxylation of dipeptides consists in *N*-halogenation of the glycine moiety. It seems that the larger van der Waals radius of bromine results in a decreased rate of *N*-bromination of the monomethoxylated product, thereby increasing the selectivity for monomethoxylation.

In the case of the methoxylation of dipeptide **1b** in the presence of NaCl (Fig. 8), the reaction yield increased up to 60% with increasing current density in the range of 0.2–2.0 A dm^{-2} and then declined above 2.0 A dm^{-2}. In the case of the methoxylation of dipeptide **1b** in the presence of NaBr (Fig. 8), the highest reaction yield (26%) was obtained at a current density of 0.2 A dm^{-2}. An increase of the current density up to 2.0 A dm^{-2} led to a slow decrease in the reaction yield. It is noteworthy that the selectivity for monomethoxylation of dipeptide **1b** was close to 100%, independent of the salt used (NaCl or NaBr). The decrease in the reaction yield above some optimal current density value at constant electric charge (2 F mol^{-1}) could be explained by assuming that the increase in the current density results in a faster recombination of the adsorbed chlorine or bromine to inactive molecular chlorine or bromine.

The influence of the concentration of sodium bromide on the reaction yield of the methoxylation of **1a** is shown in Fig. 9. An increase in the NaBr concentration from 0.004 to 0.02 mol L^{-1} caused an increase in the reaction yield. At NaBr concentrations higher than 0.02 mol L^{-1}, the yield decreased. The highest yields ($\alpha = 18\%$) were observed at a concentration of NaBr equal to 0.017 mol L^{-1}, with a

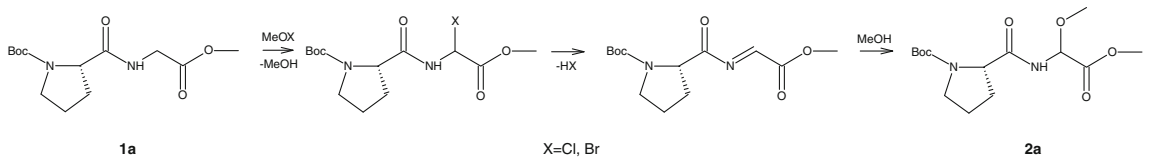

Fig. 6 α-Methoxylation of the glycine moiety in dipeptide **2a**

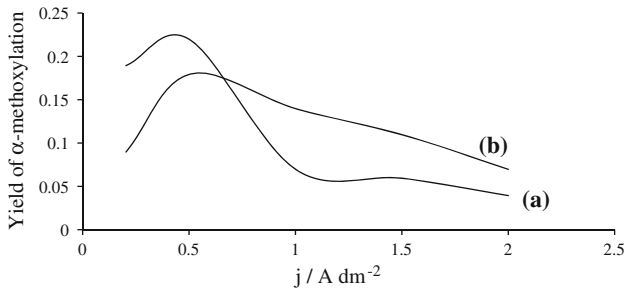

Fig. 7 Influence of current density on the yield of dipeptide **1a** monomethoxylation in the presence of NaCl (**a**) or NaBr (**b**)

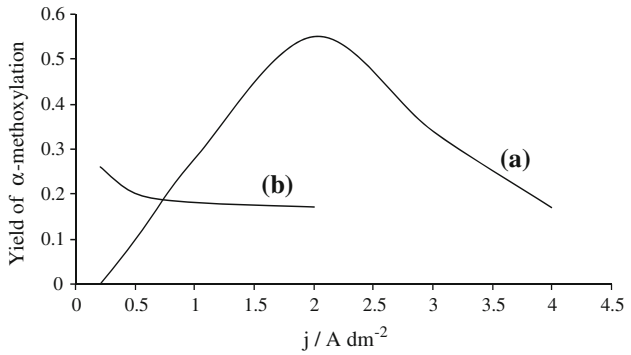

Fig. 8 Influence of current density on the yield of the dipeptide **1b** monomethoxylation in the presence of NaCl (**a**) or NaBr (**b**)

molar ratio of DIP:S = 1:1. Only about 1% of the starting dipeptide underwent dimethoxylation under these conditions. The application of too high of a concentration of sodium bromide accelerated the release of molecular bromine, which caused a brown colour and characteristic odour of the electrolyte.

Our attempts to improve the selectivity of the methoxylation of dipeptide **1a** by carrying out the electrolysis at low temperature (−20 °C) failed. Under these conditions, the reaction yield was close to zero (Table 2). Only after multiplying the electric charge four times did the reaction yield rise to 16% (NaBr) and 6% (NaCl). It seems that such a drastic decrease of the methoxylation yield arose from a decrease of dipeptide methoxylation rate at low temperature.

To test once again the aforementioned hypothesis on the formation of methyl hypohalites as intermediates in the investigated reaction, the mixture after electrolysis of dipeptide **1a** in the presence of NaBr was allowed to stand for 48 h before the work-up procedure (Table 2, entry 19). One would expect a higher reaction yield as a result of further slow halogenation of the dipeptide by the methyl hypobromite generated during the electrolysis. The result of this experiment, however, was similar to the result of experiment no. 2, in which the electrolyte was evaporated and worked-up directly after electrolysis. In the next

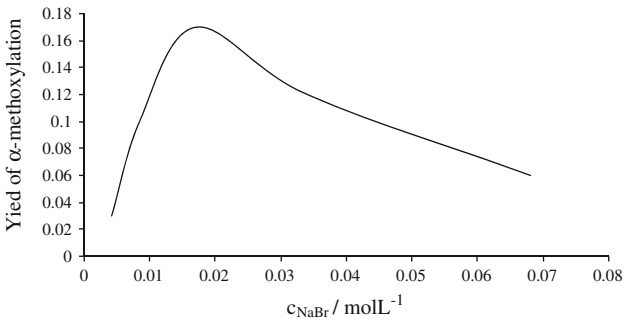

Fig. 9 Influence of the NaBr concentration on the yield of the dipeptide **1a** monomethoxylation

Table 2 Selected results of monomethoxylation of dipeptide **1a**; j = 0.5 A dm^{-2}

Entry	S	τ (min)	t (°C)	Yield of α-methoxylation (%)
15	NaBr	12	−20	<1
16	NaBr	40	−20	16
17	NaCl	12	−20	<1
18	NaCl	40	−20	6
19	NaBr	10	20	18
20	NaBr	10	20	0

experiment (Table 2, entry 20), dipeptide **1a** was added after the electric charge was applied to the electrolyte, and the obtained mixture was stirred for 15 min. In this case, we did not detect any traces of product **2a** in the reaction mixture. This indicated that the electrolyte did not contain methyl hypobromite, or that hypobromite was not able to brominate the dipeptide in these conditions. These results suggested once again that the *N*-bromination of dipeptide **1a** does not proceed in solution under the influence of methyl hypobromite, but rather at the anode surface under the influence of active atomic bromine.

Finally, taking into account the results of the experiments described above, we tried to improve the yield of the α-methoxylation of dipeptide **1a** while keeping the selectivity for monomethoxylation high. Unfortunately, increasing of the applied charge from 2 to 4 and then 6 F mol^{-1} at a molar ratio of DIP:NaBr = 1:1 and a current density of 0.5 A dm^{-2} gave again the α-methoxylation product in a yield of only about 20%, probably because of the consumption of a significant portion of the NaBr through the molecular bromine emission. Because of the undesirable consumption of sodium bromide for molecular bromine emission, we tried to increase both the electric charge and the amount of sodium bromide. We found that an applied charge of 16.7 F mol^{-1} of dipeptide at a molar ratio of NaBr:DIP = 7:1 was sufficient to achieve full conversion of the starting dipeptide, provided that NaBr was added in seven small, equal portions over equal

periods of time to keep its concentration at a low level. Further increases in the applied charge caused a decrease in yield of the monomethoxylated dipeptide and an increase in the yield of the dimethoxy derivative. By applying the aforementioned optimised conditions, we were able to obtain monomethoxylated product **2a** in a yield of 54% at a molar ratio of monomethoxylation to dimethoxylation of 1:0.25, which is markedly better result than that obtained in previous studies [8]. In the case of the methoxylation of dipeptide **1b,** we used a current density of 2.0 A dm^{-2}, a NaCl:DIP molar ratio equal to 2:1 and an applied charge of 4.7 F mol^{-1} **1b**, and we were able to obtain in these conditions monomethoxylated dipeptide **2b** in a yield of 80%, contaminated by only a trace amount of the dimethoxylated dipeptide.

4 Conclusions

Voltamperometric studies on the electrochemical α-methoxylation of Boc-Pro-Gly-OMe (**1a**) and Boc-Val-Gly-OMe (**1b**) indicated that the desorption of chlorine or bromine from the anode surface was much more effective only after the addition of dipeptide. This suggested that the dipeptide is *N*-halogenated directly by active chlorine or bromine adsorbed on the electrode surface. Further electrochemical studies revealed that the kind of mediator (NaCl or NaBr), its concentration, the current density, and the applied electric charge had a significant influence on the reaction course. In the case of dipeptide **1a**, the use of sodium bromide was necessary to obtain a relatively high ratio of α-monomethoxylation to α,α-dimethoxylation. For dipeptide **1b**, the selectivity for α-monomethoxylation was close to 100%, independently of the halogenating salt used (NaCl or NaBr). Optimisation of the selected electrolysis parameters allowed us to significantly improve the yield and selectivity of the α-methoxylation of Boc-Pro-Gly-OMe (**1a**) with respect to the literature data [8], and to obtain fairly good results in the α-methoxylation of Boc-Val-Gly-OMe (**1b**).

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