JOURNAL OF APPLIED ELECTROCHEMISTRY 18 (1988) 205–210

Electrochemical investigation on prostaglandin $F_{2\alpha}$ derivatives. I. Anodic iodination of prostaglandin $F_{2\alpha}$ and its methylesther

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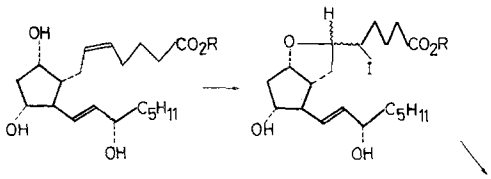
Received 28 May 1987; revised 22 August 1987

Studies of the anodic iodination of prostaglandin $F_{2\alpha}$ were carried out under a variety of electrolytic conditions. The effect of anode material, potential, pH of the electrolyte, initial substrate concentration and charge passed were investigated. A preparative technique for the iodination, in an undivided cell, has been developed. The iodinated compound – in the form of its 6-endo-(H)isomer – can be obtained in a two-electron process, with 100% conversion and nearly a quantitative product and current yield, without by-products, when using a platinum anode and cathode, +1.5 V vs SCE potential and 30 vol% methanolic 1 M aqueous citrate buffer solution (pH 3.4–3.6) containing 1–2 × 10^{-2} M of the substrate and KI as electrolyte. The method can be extended to other prostaglandin derivatives. On the basis of the experimental results a mechanism is proposed involving the iodine radical and the iodinated substrate radical as intermediates.

1. Introduction

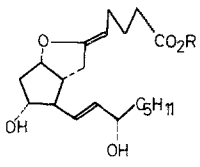
Halogenated prostaglandin $F_{2\alpha}$(2) and its derivatives are key intermediates in the synthesis of the prostacyclin compounds (3) – the highly potent substances preventing the aggregation of blood platelets. For the preparation of the halogenated $PGF_{2\alpha}$ and its derivatives a chemical method was published by Tömösközi *et al.* [1, 2] as well as an electrochemical one described by us in a Hungarian patent [3], based on a previous investigation [4].

The aim of our preliminary work was to find a simple, rapid and easily controllable electrochemical method for the halogenation of $PGF_{2\alpha}$(1), with the participation of the 9-OH group in the halogen addition reaction to the $\Delta_{5,6}$ bond of 1.



1 : R=H
1a : R=CH_3

2 : R=H
2a : R=CH_3



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Our experiments showed [4] that the iodination of $PGF_{2\alpha}$ could be carried out galvanostatically (cd 60 mA cm^{-2}) with 88% product and 83% current yield in a divided cell using platinum sheet electrodes and a potassium iodide-containing aqueous acetic acid buffer solution.

In the present paper the oxidative iodination of 1 is described having been investigated under various experimental conditions. We can report a new, convenient synthesis of 2 derivatives and provide an additional insight into the iodination mechanism.

2. Experimental details

2.1. *Materials*

Prostaglandin $F_{2\alpha}$ and its methyl esther were prepared by a method described in the literature [5, 6]. The crude products were recrystallized from ethanol. Authentic iodinated $PGF_{2\alpha}$ and its methyl esther were made as indicated earlier [1, 2]. All chemicals and solvents were commercially available, reagent grade products.

2.2. *Electrochemical equipment and procedure*

Voltammetric studies were carried out using an Elektroflex Model EF 427 potentiostat coupled to a cell of suitable geometry [7]. The same potentiostat was also employed in the preparative galvanostatic and potentiostatic tests, connected with an Elektroflex Type 1704 coulometer. All potentials were measured against a saturated calomel electrode (SCE).

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In the voltammetric tests the working microelectrode was a platinum sphere. Preparative scale experiments were performed in both undivided and divided electrolysis cell. The former was an enclosed beaker, volume about 400 cm^3, equipped with a 90 cm^2 active area Pt gauze anode, a Pt gauze cathode, an SCE electrode as reference and a magnetic stirrer. The divided cell was a simple H cell similar to that described by Lund [8], constructed of two compartments separated by sintered glass as diaphragm. The electrodes used were a platinum sheet anode (1.5 × 1.5 cm), a platinum cathode (1.0 cm^2) and a SCE as reference electrode. The volumes of the anode and cathode compartments were about 100 cm^3 respectively.

In the undivided cell the electrolyte was prepared by dissolving 4.06 × 10^{-2} M of 1 or 1a and 6.02 × 10^{-2} M of potassium iodide in 75 cm^3 of methanol and 150 cm^3 of 1 M aqueous buffer solution (pH 2.6–5.9). Composition of the buffer solutions is indicated on Table 1.

In the H cell the anolyte was prepared likewise; an aqueous acidic 1 M buffer solution was used as a catholyte without any addition. After electrolysis the pH value of the anolyte was set to pH 5 by adding diluted $NaHCO_3$ solution dropwise, under stirring, then extracted with several portions of ether. The ethereal fractions were then combined and the ether phase was dried with $MgSO_4$.

2.3. *Analysis*

The electrolyses were followed up by a thin layer chromatography (t.l.c.) on Kieselgel 60_{F254} (Merck) plates with 0.25 mm layer thickness using benzene: dioxane : glacial acetic acid (20 : 10 : 1) as eluent. The t.l.c. spots were detected with alcoholic phosphormolybdenic acid spray. Product and current yields were estimated on the basis of t.l.c. spot tests in comparison with those of the authentic samples, as well as of a material balance by analysis of products.

The identification of products was confirmed by ^{1}H-n.m.r. and ^{13}C-n.m.r. spectroscopy and comparison of the spectra with those from reference samples. The ^{1}H-n.m.r. spectra were obtained at 80 Hz and the ^{13}C-n.m.r. spectra at 20.1 MHz on a Bruker WP-80 FT n.m.r. spectrometer in $CDCl_3$ solution (in a 5 mm tube) using TMS as internal standard. The number of attached protons to carbons were gained from single-frequency off-resonance decoupling and/or gated spin-echo experiments.

Table 1. Composition of the buffer solutions

Buffer	pH[x]	*Composition for* 1 dm^3 *aqueous solution*
Glycine	2.6	glycine (113 g) + concentrated HCl (84 cm^3) + water
Citrate I	3.1	citric acid (315 g) + KOH (28 g)
Citrate II	3.4	citric acid (315 g) + KOH (56 g)
Citrate III	4.4	citric acid (210 g) + KOH (74 g)
Citrate IV	4.8	citric acid (210 g) + KOH (91 g) + concentrated HCl (5 cm^3)
Acetate I	4.9	acetic acid glacial (90 cm^3) + KOH (28.5 g)
Acetate II	5.6	acetic acid glacial (90 cm^3) + KOH (56 g)
Succinic acid	5.9	succinic acid (116 g) + KOH (86 g)

[x] pH values measured in the solution to be used.

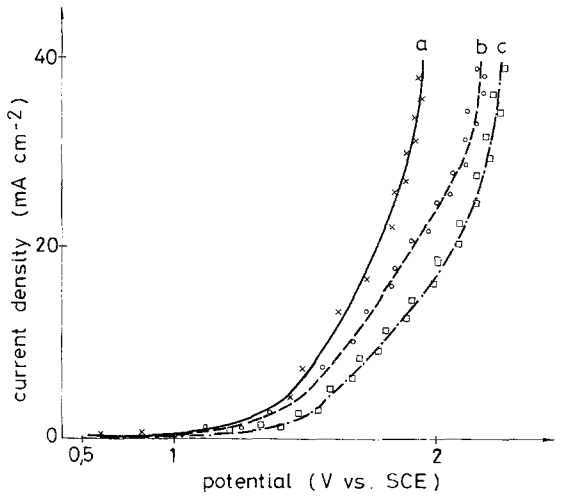

Fig. 1. Polarization curves for prostaglandin $F_{2\alpha}$ (10 mM) and its iodinated derivative (10 mM) at a Pt anode in 30 vol % methanolic acetate (1 M) buffer solution (pH 4.9). (a) Background; (b) $PGF_{2\alpha}$; (c) iodinated $PGF_{2\alpha}$.

3. Results and discussion

3.1. *Voltammetric studies*

The steady state *I–E* curves obtained for the direct oxidation of 1 and its iodinated derivative 2 at a Pt anode, in methanolic acetate buffer solution (pH 4.9) are shown in Fig. 1. It can be seen that the addition of 1 and 2 does not depolarize the anode, but shifts the curve in the anodic direction. Therefore 1 and 2 may clearly not be oxidized before oxygen evolution occurs, also the direct oxidation of the starting material as well as the product is not feasible, although the inflection in curve (b) suggests also some direct $PGF_{2\alpha}$ oxidation. On the other hand, since the

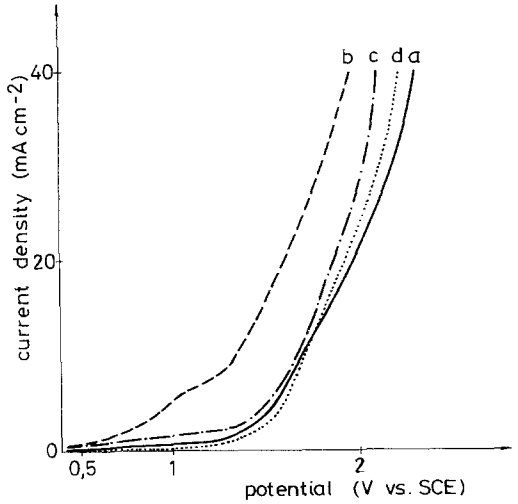

Fig. 2. Polarization curves of halide ions at a Pt anode in 30 vol % methanolic acetate buffer (1 M) solution (pH 4.9). (a) Background; (b) 10 mM KI; (c) 10 mM KBr; (d) 10 mM KCl.

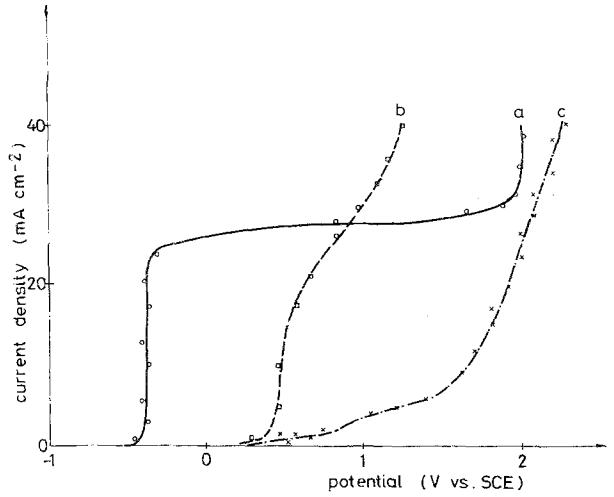

Fig. 3. Polarization curves for prostaglandin $F_{2\alpha}$(10 mM) at different anodes in 30 vol % methanolic acetate buffer (1 M) solution (pH 4.9), containing KI (10 mM). (a) Pb; (b) graphite; (c) Pt.

current density of curves (b) and (c) is weaker than that of curve (a) (between 0.5 and 1.8 V) this suggests that the adsorption of 1 or 2 occurred.

Fig. 2 shows *I–E* curves of the three halide ions (Cl^-, Br^- and I^-) under the same conditions. As can be seen, the Cl^-/Cl_2 redox system may not be suitable for the oxidation, because the oxidation potential of the Cl^- ions is too close to that of oxygen evolution (background). Both I^-/I_2 and Br^-/Br_2 seem to be good redox systems in slightly acidic solutions, as iodide and bromide ions are much more easily oxidized than are 1 and 2. However, since iodide ions are oxidized to an active iodine species at much lower potential, the reaction of 1 with the electrogenerated iodine was studied in more detail.

Fig. 3 shows a comparison of the steady state *I–E* curves at Pt, Pb and graphite anodes for 1 in methanolic acetate buffer solution containing KI. As long as the anode is made of an inert material it is to be expected that the working electrode reaction in the iodide solution would be the formation of iodine,

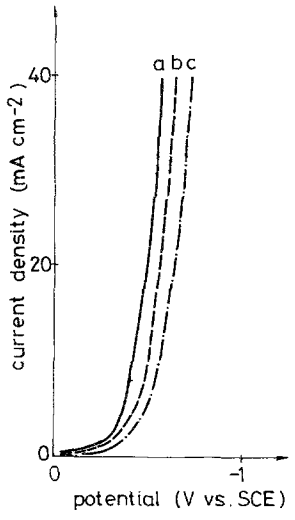

Fig. 4. Polarization curves for the reduction of prostaglandin $F_{2\alpha}$(10 mM) and its iodinated derivative (10 mM) at a Pt cathode in 30 vol % methanolic acetate buffer (1 M) solution (pH 4.9), containing KI (10 mM). (a) Background; (b) $PGF_{2\alpha}$; (c) iodinated $PGF_{2\alpha}$.

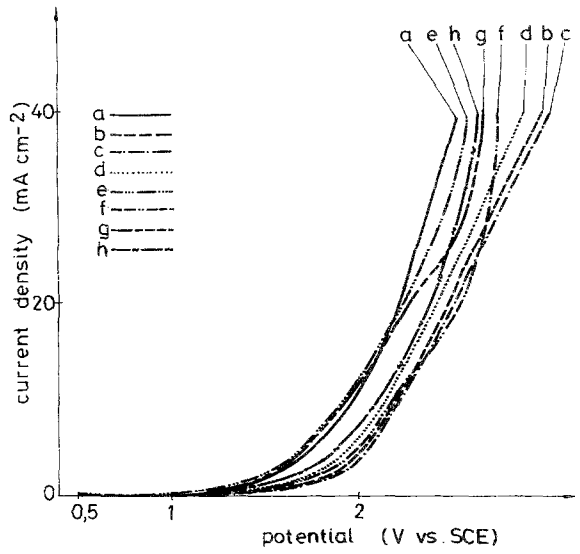

Fig. 5. Polarization curves for prostaglandin $F_{2\alpha}$ (10 mM) at a Pt anode in different (30 vol % methanolic, aqueous, buffer (1 M)) solutions containing KI (10 mM). (a) pH 2.6; (b) pH 3.1; (c) pH 3.4; (d) pH 4.4; (e) pH 4.7; (f) pH 4.9; (g) pH 5.6; (h) pH 5.9.

the standard potential for which is +0.293 V (SCE). Fig. 3 clearly indicates that the anodic process on Pb electrode is the oxidation of PbI_2, the reversible potential for this reaction is about −0.6 V (SCE), close to the value observed.

I–E curves for the reduction of 1 and 2 at a Pt cathode are displayed in Fig. 4. This suggests that the main reaction here is hydrogen evolution, since polarographic experiments (data not shown) showed that 1 and 2 are reducible only at a Hg cathode. Therefore neither of the above mentioned compounds can be easily reduced and both are stable under these conditions. This one was one of the *sine qua* non requirements for the planned undivided cell operations.

All the polarization curves at a Pt anode plotted in different buffer solutions (Fig. 5) are similar, that is

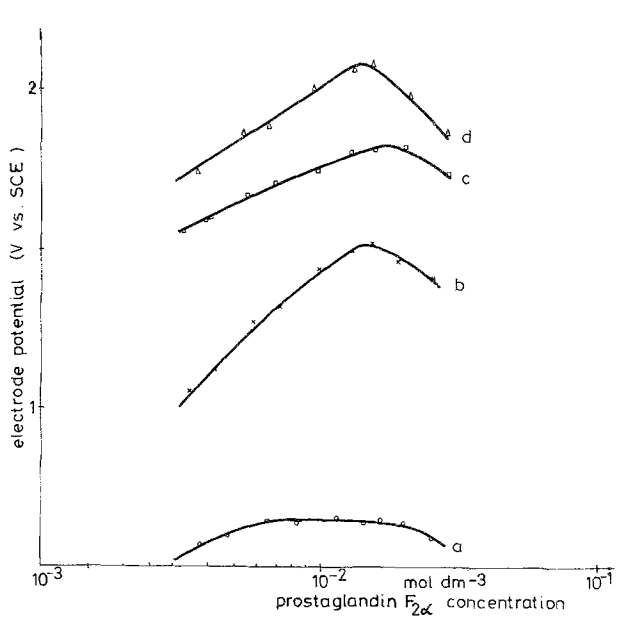

Fig. 6. Electrode potential (V vs SCE) as a function of prostaglandin $F_{2\alpha}$ concentration (mol dm^{-3}) at different current densities. (a) 2 mA cm^{-2}; (b) 4 mA cm^{-2}; (c) 12 mA cm^{-2}; (d) 20 mA cm^{-2}.

the oxidation process (up to the oxygen evolution) seems to be independent of the pH values of the electrolytes. Since the starting material (1) cannot be oxidized in the 0–1.8 V potential range between pH 2–6, the product of 2 can be formed without the oxidation of 1. However, mixing the iodine solution and that of 1 without electrolysis, did not form any appreciable amount of 2. Therefore the anodically formed iodine radical seems to react with 1 to form 2.

Fig. 6 gives a plot of electrode potential (V) against starting material (1) concentration in a semi-logarithmic form at different current densities. It can be seen that the steady state current as well as the electrode potential is proportional to the concentration of 1, with well defined linear regions at lower current densities. The rising part of the E-log c plots is evidence for $PGF_{2\alpha}$ adsorption, causing increasing blocking of anodic reactions on the Pt surface. On the other hand from these data it can be concluded that during the electrolysis the electrode potential will change due to consumption of 1 and formation of 2. This can be corrected by means of controlling the anode potential, or, if the electrolysis is conducted galvanostatically, by means of periodical additions of 1 to the electrolyte.

3.2. *Preparative electrolyses*

A preparative scale electrolysis requires a high current density and this is dependent on a high concentration of substrate. The solubility of 1 is enhanced by increasing the percentage of solvent or the temperature. The solvent system found most suitable from the viewpoint of starting material and product solubility, conductivity and current efficiency was ethanol or methanol in max. 30 vol % concentration. Above 40% alcohol, the selectivity of the reaction seriously diminishes and at 50% the electrolysis is difficult because of the low conductivity. The reaction temperature must lie between 20 and 35° C, as high temperature favours the formation of by-products.

A series of CPE at a Pt gauze anode and cathode, in an undivided cell were carried out to define how the products depend on the electrolysis parameters. The effects of the pH and the applied electrode potential are shown by the results in Table 2, for electrolyses in different aqueous methanolic buffer solutions (pH 2.6–5.9). The products are reported when the electrolyses had been terminated after the passage of 2.5 F mol^{-1} of 1.

It can be seen that the best product and current yield of 2 can be obtained when using citrate II buffer solution (pH 3.4) at a potential of 1.4 V vs SCE. Some further experiments carried out in a narrower potential range (between 1.0 and 1.8 V vs SCE), in the above mentioned electrolyte (see Table 3), show that it is possible to define the 1.5 V potential, where both the organic and current yield of 2 is high. At more positive potentials oxygen evolution occurs, but while this adversely affects the current efficiency, it does not decrease the selectivity of formation of 2. Indeed, in a further experiment carried out at a constant current density of 12 mA cm^{-2} for 1, at Pt, the current

Table 2. Effect of pH and potential on the electrolytic iodination of prostaglandin $F_{2\alpha}$ (10 mM) in different, 30 vol % methanolic, aqueous buffer (1 M) solutions containing KI (10 mM). Anode: Pt. Electrolyses terminated after the passage of 2.5 F mol^{-1} of $PGF_{2\alpha}$

pH *of the electrolyte*	*Potential* (V vs SCE)	*Product yield* (%)	*Current yield* (%)	*Comments*
2.6	1.0	46	36.8	side products
	1.4	71	56.8	
	1.8	38	30.4	
3.1	1.0	87	69.6	traces of side products
	1.4	96	76.8	
	1.8	85	68.0	
3.4	1.0	93	74.4	no side products
	1.4	90	78.4	
	1.8	91	72.8	
4.4	1.0	86	68.8	traces of side products
	1.4	93	74.7	
	1.8	81	64.8	
4.8	1.0	86	68.8	side products
	1.4	90	72.0	
	1.8	83	66.4	
4.9	1.0	85	68.0	side products
	1.4	88	70.4	
	1.8	82	65.6	
5.6	1.0	84	67.2	side products
	1.4	86	68.8	
	1.8	80	64.0	
5.9	1.0	70	56.0	side products
	1.4	77	61.6	
	1.8	71	56.8	

Table 3. The effect of the anodic potential on the electrolytic iodination of prostaglandin $F_{2\alpha}$ (10 mM) in 30 vol% methanolic citrate (1 M) buffer (pH 3.4) solution containing KI (10 mM). Anode: Pt. *Electrolyses terminated after the passage of 2.5 F mol^{-1} of $PGF_{2\alpha}$*

Potential (V vs SCE)	*Product yield* (%)	*Current yield* (%)
1.3	97	77.6
1.5	99.5	79.6
1.6	97	77.6
1.7	93	74.4

efficiency dropped to 47%, but the organic yield of 2 was still 87%.

CPE were carried out at various concentrations of 1. The results are reported in Table 4. It can be seen that the product and current yield of 2 is independent of the concentration of 1 between 0.005 and 0.02 M, that is approximately around the plateau of the *E*-log *c* curves (see Fig. 6), but decreases above it, presumably due to the enhanced oxygen evolution.

Data from further CPE experiments, performed in an undivided cell using the best electrolysis conditions found so far showed that the product yield and the extent of conversion were the same, almost 100%, indicating the absence of side reactions. $PGF_{2\alpha}$ could not be found in the electrolyte after 2.0 F mol^{-1} of charge passed. The influence of the process parameters (Tables 1–4) on the product yield indicate the following optimum conditions for the maximum product yield: medium 30 vol% methanol in 1 M aqueous citrate buffer solution (pH 3.4); 1–2 × 10^{-2} substrate and KI respectively; undivided cell, anodic potential 1.5 V vs SCE; Pt anode, charge 2.0 F mol^{-1} and temperature 20–35° C.

3.3. *Product analysis*

The structure of the isolated electrolysis product 2 and 2a, prepared as indicated above, was demonstrated by ^{1}H- and ^{13}C-n.m.r. data (Tables 5 and 6).

From the ^{1}H-n.m.r. spectrum (Table 5) it can be seen that the main component of the isolated electrolysis product 2 is the 6-endo 'iodine-ether' isomer. The 6-endo-(H) isomer construction is proved by the 9-H chemical shift, since in the exo-isomer this value

Table 5. ^{1}H-n.m.r. data of the electrolytic iodination products of prostaglandin $F_{2\alpha}$ (in $CDCl_3$; TMS = 0.00 p.p.m.)

5.55 m (2); 13, 14 – H
4.57 m (1); 9 – H
3.6 – 4.25 m (4); 5, 6, 11, 15 – H
1.05 – 2.65 m (20); 8, 12 – H
2, 3, 4, 7, 10, 16, 17, 18, 19 – H_2
0.90 t (3); 20 – H_3

is 4.35 [9]. However, this is in accordance with the ^{13}C-n.m.r. data.

The assignment of the ^{13}C-n.m.r. spectra of 2, prepared by broad frequency proton decoupling, in $CDCl_3$, show that the comparison of the C-5 and C-9 chemical shifts with similar data of the exo/endo-isomer pairs of analogous compounds [10] prove that the main component was a 6-endo configuration.

On the basis of the n.m.r. spectra it is evident that the exo/endo-isomer ratio in both the chemically and electrochemically iodinated product is exactly the same, although the latter is free from any impurity. The anodic iodination process can be performed likewise, starting from the methyl esther derivative of $PGF_{2\alpha}$(la).

3.4. *Reaction mechanism*

On the basis of potentiodynamic investigations, CPE and product analysis, a reaction scheme has been proposed for the anodic iodination process.

This mechanism consists of an initial one-electron step to form the iodine radical:

$$I^- - e^- \rightarrow I^{\cdot}$$

which reacts, in a chemical reaction, with the substrate, to produce the iodinated substrate radical:

$$I^{\cdot} + R \rightarrow I{-}R^{\cdot}$$

where R is 1 or la.

The iodinated substrate radical (I–R$^{\cdot}$) is electroactive and loses one electron and one proton to give the iondinated compound 2 or 2a:

$$I{-}R^{\cdot} - e^- \rightarrow R{-}I + H^+$$

The overall two electron process is as follows:

$$R + I^- - 2e^- \rightarrow R{-}I + H^+$$

Table 4. Anodic iodination of prostaglandin $F_{2\alpha}$ at a Pt anode in 30 vol% methanolic citrate (1 M) buffer solution (pH 3.4). Anodic potential: (1.5 V vs SCE). *Electrolyses terminated after the passage of 2.2 F mol^{-1}*

Concentration of prostaglandin $F_{2\alpha}$ (mmol dm^{-3})	*Initial current density* (mA cm^{-2})	*Product yield* (%)	*Current yield* (%)
5	6	99.2	90.2
10	45	99.6	90.5
20	130	98.6	89.6
50	200	80	72.7

Table 6. ^{13}C-n.m.r. data of the electrolytic iodination products of prostaglandin $F_{2\alpha}$ (in $CDCl_3$; TMS = 0.00 p.p.m.)

C-atoms	*Peak frequency*	*C-atoms*	*Peak frequency*
C – 1	176.7	C – 5, C – 10	40.6
C – 14	135.8	C – 16	36.9
C – 13	132.4	C – 4	36.1
C – 6	81.2	C – 7	36.0
C – 9	81.1	C – 2	33.7
C – 11	76	C – 18	31.7
C – 15	73.1	C – 3, C – 17	25.1
C – 12	55.0	C – 19	22.5
C – 8	47.5	C – 20	14.0

4. Conclusion

On the basis of potentiodynamic as well as CPE studies, a general method has been presented for the iodination of $PGF_{2\alpha}$ and its methyl esther derivative. Moreover, the method can be extended to other prostaglandin compounds and to the iodination of different substrates. Advantages of this approach to electrochemical synthesis include a nearly quantitative product and current yield, 100% conversion without by-products.

The most important finding of this investigation is the necessity to keep the anodic potential below a critical value (< 1.8 V). Best performance is obtained by using an undivided cell and an alcoholic citrate buffer solution (pH 3.4–3.6).

All the evidence suggests that the reactions proceed by an indirect oxidation ($I^- \rightarrow I^{\cdot}$) initiated direct one-electron step on the substrate, combined with proton abstraction. Therefore the overall process consumes $2F\,mol^{-1}$.

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