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Electrochemical investigation on prostaglandin $F_{2\alpha}$ derivatives. II. Cathodic reduction of the iodinated prostaglandin $F_{2\alpha}$ and its methyl ester

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Based on voltammetric studies, preparative controlled potential reduction on an Hg cathode of iodinated $PGF_{2\alpha}$ (IPG) resulted in the production of either $PGF_{2\alpha}$ (nearly quantitatively) or $PGF_{2\alpha}$ and the biologically active PGI_1 (in a 2 : 3 ratio at maximum), depending on the medium and the potential used. The 5-Z isomer percentage in the $PGF_{2\alpha}$ thus formed varied between 50 and 60, while originally, before the anodic iodination and the subsequent reduction of IPG, this ratio was 98%. The electrochemically formed PGI_1 contained 95% 6-S and 5% 6-R isomer. In any selected medium the first voltammetric wave can be ordered to $PGF_{2\alpha}$ formation, and that of the second wave (in aqueous and non-aqueous media) to PGI_1 formation. On the basis of the experimental results a mechanism is proposed for the electroreduction process in aqueous media.

1. Introduction

As part of a broad programme whose main aim is to explore the possibilities of converting electrochemically the prostaglandin compounds to biologically active materials, we have used the iodinated prostaglandin $F_{2\alpha}$ (IPG) and its methyl ester (Me-IPG) isomers, the key intermediates in the synthesis of prostacyclin compounds, as feedstocks. The first paper in this series discussed the effect of electrolysis parameters on the yield for iodination of $PGF_{2\alpha}$ [1]. These studies had the objective of improving the yields compared to those reported in the earlier papers [2, 3] and, indeed, it was shown that by careful selection of the electrolysis conditions almost quantitative product and current yield of the iodinated derivative could be obtained from the iodination of $PGF_{2\alpha}$.

The aim of the present work has been to determine the feasibility of the electrochemical reductive elimination of the iodine from IPG and Me-IPG for producing useful pharmaceuticals. Examination of the literature suggests that this particular reaction has not been studied electrochemically.

In this paper we report the study of the cathodic reduction of IPG in slightly acidic, neutral and basic aqueous as well as organic media and discuss the effect of various electrolysis parameters on both the voltammetric properties and the products. The objective was to seek conditions where products could be isolated in good yield and the electrolysis carried out effectively.

2. Experimental details

2.1. *Materials*

IPG and Me-IPG were prepared electrochemically as a mixture of isomers (95%, 5S, 6S; 5% 5R, 6R) by a method described in our previous paper [1]. Products of the cathodic reduction were compared to authentic samples made as indicated earlier [2, 3].

All chemicals and solvents used were commercially available, reagent grade products and the water was doubly distilled. The acetonitrile (MeCN), a Fluka product, was purified by a method of O'Donnell *et al.* [4]. Commercial *N*, *N*-dimethylformamide (DMF) was distilled at 20 mmHg and dried over 4 Å molecular sieves just before each experiment [5]. Tetrabutylammoniumperchlorate (TBAP), as well as tetrabutylammoniumiodide (TBAI), were also employed, both being Fluka products, subjected to further purification by known methods and their purity checked by chromatography.

Buffer solutions were prepared from analytical reagent grade chemicals; their composition is presented in Table 1. The mercury and nitrogen were purified by standard techniques.

2.2. *Electrochemical equipment and procedure*

Polarograms were recorded on a Radiometer PO4 polarograph with a capillary of $m = 1.82\,mg\,s^{-1}$ and a drop time $t = 4.65\,s$, with a two-electrode arrangement using a Kalousek cell in a 1.4×10^{-3} M solution

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Table 1. Composition of buffer solutions

Name of buffer	*pH*[1]	*Composition for 1 dm³ aqueous solution*
Hydrochloric acid	0.8	Conc. HCl (333 cm³)
Glycine	2.1	Glycine (113 g) + conc. HCl (84 cm³)
Citrate	3.1	Citric acid (315 g) + KOH (28.5 g)
Acetate I	4.9	Acetic acid glacial (90 cm³) + KOH (28.5 g)
Acetate II	5.6	Acetic acid glacial (90 cm³) + KOH (57 g)
Succinic acid	5.9	Succinic acid (116 g) + KOH (86 g)
Phosphate I	6.9	KH_2PO_4 (102 g) + $Na_2HPO_4 . 2H_2O$ (44.5 g)
Phosphate II	7.4	KH_2PO_4 (136 g) + K_2HPO_4 (174 g)
Phosphate III	7.7	KH_2PO_4 (34 g) + $Na_2HPO_4 . 2H_2O$ (133.5 g)
Tris	8.0	Tris-(hydroxymethyl)-aminometan (60 g) + conc. HCl (25 cm³)
Borate I	9.1	Boric acid (72 g) + KOH (13 g)
Borate II	10.0	Boric acid (60 g) + KOH (28.5 g)
Borate III	11.1	Boric acid (84 g) + KOH (59 g)
Phosphate IV	11.3	$Na_2HPO_4 . 2H_2O$ (89 g) + $Na_3PO_4 . 12H_2O$ (95 g)
Phosphate V	12.5	$Na_2HPO_4 . 2H_2O$ (35.5 g) + $Na_3PO_4 . 12H_2O$ (190 g)
Potassium hydroxide	13.4	KOH (112 g)

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

of IPG. The solution to be polarographed (25 cm³) contained ethanolic stock solution of IPG (2 cm³), aqueous buffer solution (5 cm³), ethanol (10 cm³), saturated KCl (0.5 cm³) and water. The concentration of the stock solution of IPG was 1.7×10^{-2} M.

Cyclic voltammetry was carried out using an Elektroflex Mod. EF 427 type potentiostat coupled to an Elektroflex Mod. EF-1808 voltage scan generator and results recorded on an EMG Mod. NE-230 type *x–y* chart recorder. In these experiments a cell of suitable geometry was employed [6]. A hanging mercury drop (HMDE) working electrode, a Pt wire counter electrode and an Ag/AgI reference electrode (in 0.1 mol dm^{-3} TBAI in DMF) were used in this cell. The electrolyte consisted of DMF containing 0.1 M TBAI and 4×10^{-3} M of IPG.

In macro-scale preparative electrolyses a potentiostat mentioned earlier with an associated coulometer (Elektroflex Mod. EF-1704) was used. In these tests an H cell similar to that described by Lund [7] was employed, using a mercury pool working electrode (area: 12 cm²) and a Pt sheet auxiliary electrode (area: 4 cm²), the latter being separated from the main compartment by two coarse sintered glass discs. Stirring was accomplished by using a magnetic stirrer bar, as well as by degassing with nitrogen during the electrolysis. In the macro-scale electrolyses carried out in aqueous solutions, all the reported potential values were referred to a saturated calomel electrode (SCE), while in non-aqueous systems the potentials were measured against an Ag/AgI reference electrode indicated earlier. All experiments were carried out at room temperature.

In a typical run 100 mg (4.5×10^{-3} M) IPG or Me-IPG was dissolved either in ethanol (15 cm³) and aqueous buffer solution (25 cm³) or, when electrolyses were performed in non-aqueous systems, in DMF or MeCN containing 0.1 M TBAI (40 cm³). These solutions served as catholytes. The anodic compartment of the H cell contained the same solutions as the catholyte without IPG or Me-IPG.

After electrolysis the catholyte was separated from mercury, its pH value was set to pH 5 either with diluted HCl or $NaHCO_3$ solution, then extracted with several portions of ether. The ethereal fractions were combined and the ether phase was dried with $MgSO_4$.

2.3. *Analysis*

The electrolyses were followed up by thin layer chromatography (TLC) using a method described in our earlier paper [1]. The reaction products were separated by preparative TLC. Product and current yield were estimated on the basis of TLC spot tests in comparison with those of the authentic samples, as well as of a material balance by analysis of products and also by product isolation.

The identification of products was confirmed by ^{1}H- and ^{13}C-NMR as well as with IR and MS spectrometry. The ^{1}H-NMR spectra were obtained at 80 Hz and the ^{13}C-NMR spectra at 20.1 MHz on a Bruker WP-80 FT NMR spectrometer in $CdCl_3$ solution (in a 5 mm tube) using TMS as internal standard. The number of attached protons to carbons was gained from gated spin echo experiments. The IR spectra were recorded by a Spectromom 2000 IR spectrometer, and the MS spectra by a JEOL 01SG-2 type spectrometer.

3. Results and discussion

The electrochemical reduction of various organic halides has been studied extensively, employing mainly polarographic techniques in aqueous systems, at a mercury electrode [8]. A few attempts were made to isolate and/or analyse products obtained from the cleavage of carbon–halogen bonds as well as to elucidate the mechanism of the reduction. Barclay [9] found that the adsorption prior to the reduction may play an important role in halide reduction. In a number of electrochemical reductions of activated organic halides coupled products were observed [10].

Table 2. Polarographic behavior of iodinated $PGF_{2\alpha}$ in aqueous solutions

Name of buffer	*pH*	$E_{1/2}$ (*V*)		i_d^c (μA)	
		I	*II*	*I*	*II*
Hydrochloric acid	0.8	1.0		4.9	
Glycine	2.1	1.16		5.3	
Citrate	3.1	1.17		5.0	
Acetate I	4.9	1.25		4.6	
Acetate II	5.6	1.25		4.8	
Succinic acid	5.9	1.25		4.9	
Phosphate I	6.9	1.26	1.56	5.6	2.6
Phosphate II	7.4	1.27	1.58	4.9	2.7
Phosphate III	7.7	1.28	1.37	4.8	2.1
Tris	8.0	1.28	1.59	4.6	2.1
Borate I	9.1	1.26	1.59	4.7	2.4
Borate II	10.0	1.28	1.57	4.2	2.0
Borate III	11.1	1.29	1.60	5.1	2.4
Phosphate IV	11.2	1.30	1.58	4.9	2.3
Phosphate V	12.5	1.28	1.60	5.3	2.4
Potassium hydroxide	13.4	1.29	1.59	5.2	2.5

i_d^c maximum current.

3.1. *Polarography*

During the course of our study the polarographic technique was employed in aqueous solutions. The polarograms were recorded over the entire pH range for selecting the best medium and pH values for controlled potential electrolyses.

The polarographic experiments show (see Table 2) that IPG is reducible in all buffer compositions and pH ranges studied, above pH 7 in two consecutive steps. The half-wave potential ($E_{1/2}$) values of the first polarographic wave (Fig. 1a) shifted slightly to more negative potentials with an increase of pH up to about 7; above this value the $E_{1/2}$ of both waves (a and b) have been found to be nearly independent of pH. This phenomenon indicates the participation of two electrode processes above pH 7, of which neither involves a proton transfer prior to electron transfer, characterizing the halogenated hydrocarbons [11]. The wave height values were also independent of the pH. The ratios of the two wave heights (i_a/i_b) were found to be constant (about 2). With increasing concentration of IPG around the region of 10^{-3} M, the first polarographic wave moved to more cathodic potentials.

3.2. *Cyclic voltammetry*

The cyclic voltammogram for IPG, recorded with 400 mV s^{-1} scan rate between 0.3 and 2.3 V on an HMDE electrode in DMF/TBAI electrolyte, shows one reduction wave around 1.4 V and an unusual feature of an inverted wave in the reverse (oxidation) sweep around 1.9 V vs the Ag/AgI electrode (Fig. 2). Inverted waves, obtained in the cyclic voltammograms

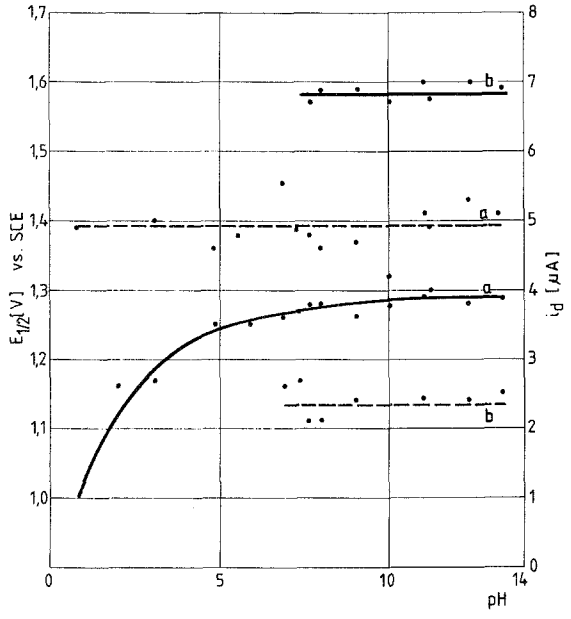

Fig. 1. Variation of the half-wave potentials (solid line) and wave heights (dashed line) with the pH of the polarographic waves of iodinated $PGF_{2\alpha}$ in aqueous buffered solutions at 25° C.

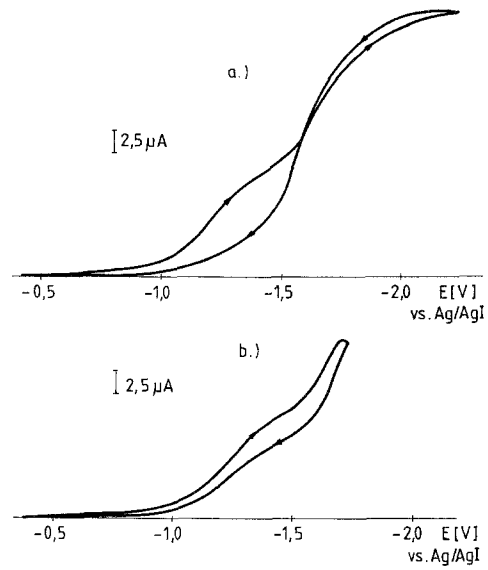

Fig. 2. Cyclic voltammogram of iodinated $PGF_{2\alpha}$ (4×10^{-3} M) in DMF/TBAI (0.1 M) at HMDE. Scan rate: 0.4 V s^{-1}. (a) 0.3–2.3 V; (b) 0.3–1.7 V.

Table 3. Results of the preparative controlled potential reduction of iodinated $PGF_{2\alpha}$

Medium	*pH*	*Applied potential (V vs SCE)*	*% Conversion*	*Product yields*		*Current efficiency (%)*
				$PGF_{2\alpha}$	*PGI_1*	
Hydrochloric acid	0.8	1.0	99	99	–	89
Glycine	2.1	1.16	99.8	99.6	–	89
Citrate	3.1	1.17	99.5	99	–	91
Acetate I	4.9	1.25	99	99	–	90
Acetate II	5.6	1.25	100	99.8	–	93
Succinic acid	5.9	1.25	99.8	99.2	–	92
Phosphate I	6.9	1.26	99.5	99	–	90
		1.56	99	58	41	84
Phosphate II	7.4	1.27	99.5	99	–	85
		1.58	99.8	40	59	85
Phosphate III	7.7	1.28	99	98	–	89
		1.57	100	47	52	86
Tris	8.0	1.28	99.2	90	–	88
		1.59	99.8	39	60	85
Borate I	9.1	1.26	99.2	99	–	87
		1.59	99.5	40	58	85
Borate II	10.0	1.28	100	99	–	87
		1.57	99.5	41	58	85
Borate III	11.1	1.29	99.2	98.7	–	89
		1.60	100	38	61	84
Phosphate IV	11.2	1.30	99.6	99	–	89
		1.58	99	49	49	84
Phosphate V	12.5	1.28	99.5	98	–	86
		1.60	99	50	48	84
KOH	13.4	1.29	99	97	–	89
		1.59	99.5	59	40	83
DMF/TBAP		1.4	99.5	87	–	30[1]
		1.9	99	47	39	74[1]
MeCN/TBAP		1.4	99.5	91	–	81[2]
		1.9	99	41	47	78[2]

[1] Side products.
[2] Traces of side products.

of other compounds [12, 13], were explained by an interaction of the second wave reduction products with the electrode (Hg) and the electrolyte. This explanation seems to be feasible in our case too, proved by the wave-clipped voltammogram of IPG, recorded in the potential range 0.3–1.7 V (Fig. 2b) where no inverted wave was seen.

From the above experiments it was concluded that non-aqueous electrolytes were also suitable for the cathodic reduction of IPG and both 1.4 and 1.9 V could be chosen for potential control.

3.3. *Preparative experiments*

A large number of controlled potential electrolyses (CPE) were carried out at an Hg cathode in different aqueous buffered and non-aqueous systems. The polarographic half-wave potentials or the two cyclic voltammetric wave potentials (1.4 and 1.9 V) were selected for CPE.

In all cases two main products **1** and **2** were identified by TLC spot tests. The mixture of the two isolated electrolysis products showed considerable prostacycline (PGX)-like biological activity, therefore the two products were separated by preparative TLC Anti-coagulant activity in the electrolyte was 91.1% in $10\,\mu g\,cm^{-3}$ concentration and, after separation of product **2** from the electrolyte, this activity changed to 50% in $1\,\mu g\,cm^{-3}$ concentration, measured by the method of Born [14].

In comparison with that of the authentic sample it was proved that product **1** was $PGF_{2\alpha}$, in which the 5-Z isomer percentage varied between 50 and 60% and that of the 5-E isomer between 40 and 50%, measured by liquid chromatography [15]. It should be mentioned that originally, before the anodic oxidation of the $PGF_{2\alpha}$ [1] and the subsequent reduction of its iodinated product IPG, the 5-Z isomer percentage was 98%.

The biologically active product **2** was identified by spectroscopic methods. The ^{1}H- and ^{13}C-NMR spectra show that it was a mixture of isomers. The sample was converted into its methyl ester and this derivative was separated into two fractions by TLC. The major compound was identified as 6-S PGI_1, the minor as 6-R PGI_1, based on the agreement of their MS and ^{1}H-NMR spectra with reported literature data of these compounds [16, 17]. The ^{1}H-NMR spectra of **2**, prepared before the product separation, showed that about 95% of **2** was the 6-S isomer.

The main results of our studies are summarized in Table 3. From the data it is clear that the ratio of the electrolysis products $PGF_{2\alpha}$ and PGI_1 was the function of the medium and the potential applied. In aqueous

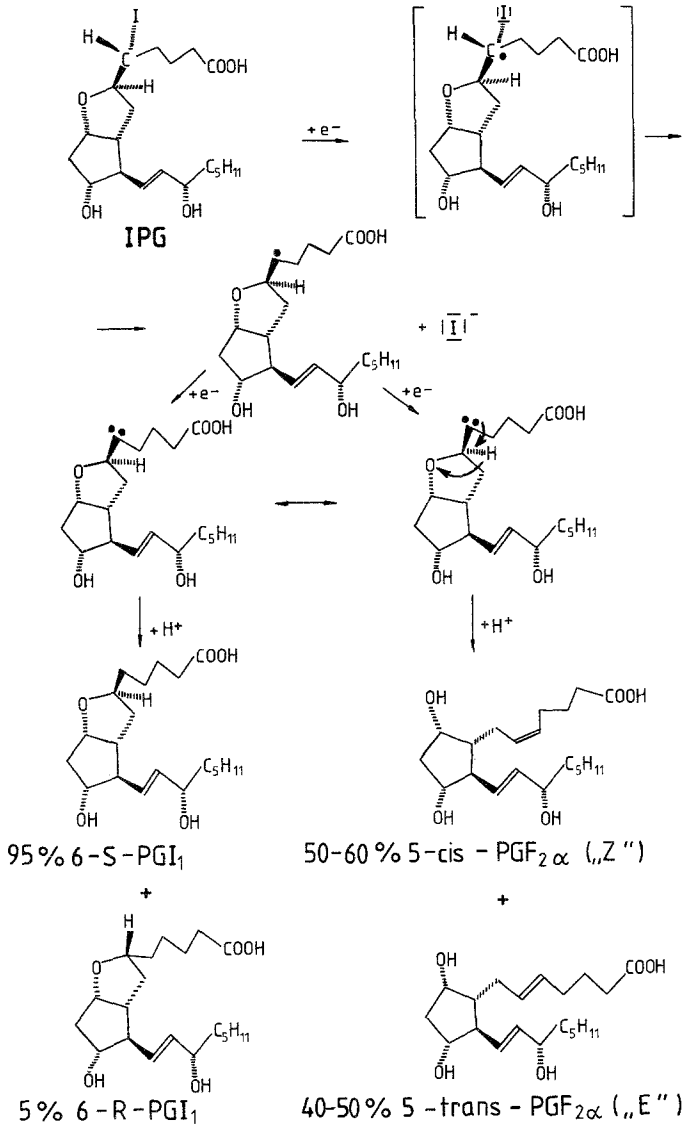

Fig. 3. Proposed reaction mechanism of the electrochemical reduction of iodinated $PGF_{2\alpha}$ in aqueous media.

acidic media at any selected potentials, in alkaline aqueous and non-aqueous solutions at the first polarographic or cyclic voltammetric wave potentials, only $PGF_{2\alpha}$ was formed nearly quantitatively, while at the second voltammetric wave potentials the electrolysis products were both $PGF_{2\alpha}$ and PGI_1. Therefore the first voltammetric wave can be ordered to $PGF_{2\alpha}$ formation and that of the second wave to PGI_1 formation.

The total number of electrons (n_{app}) involved in the reduction at the first voltammetric wave (obtained by macroscale CPE) was 1.75–1.98, independent of the medium, while that of the second wave was 2.05–2.45. Therefore the two polarographic waves, seen at higher pH values, both correspond to a nearly two-electron process. The enhancement of the second polarographic wave current, that is the 2:1 ratio between the two polarographic currents, may be explained by potential-dependent adsorption of IPG at the Hg electrode surface.

The best possible product yields (60%) and current efficiencies (51%) for PGI_1 production were achieved when the electrolyses were carried out at the second polarographic waves in aqueous alkaline buffered solutions in the pH region 7–11. Performing the electrolyses in non-aqueous electrolytes potentiostatically or in aqueous electrolytes galvanostatically, the yields of $PGF_{2\alpha}$ and PGI_1 were about the same as mentioned above, but the current efficiencies diminished considerably, presumably owing to side reactions. Similar phenomena were observed when a lead or cadmium cathode was used.

The cathodic reduction can be carried out likewise, starting from the methyl ester derivative of IPG.

3.4. *Reaction mechanism*

In the present work no attempt was made to study reaction mechanisms other than by examination of the type of products formed. The mechanistic conclusions are therefore tentative and only generalized schemes can be suggested (see Fig. 3).

In aqueous alkaline media the initial, one-electron step produces a free radical and an iodide ion through the decomposition of the intermediate anion radical. The free radical takes up another electron quickly to give the substrate anion which can be described by two resonance forms shown in Fig. 3, depending on the localization of the lone electron pair. The protonation of these carbanion intermediates results in either

$PGF_{2\alpha}$ or $PGF_{2\alpha}$ and PGI_1 formation, depending on the pH and potential.

4. Conclusion

Voltammetric and CPE studies resulted in a method for the electrochemical reduction of iodinated $PGF_{2\alpha}$ and its methyl ester derivative. Depending on the electrolysis parameters either $PGF_{2\alpha}$ (nearly quantitatively) or $PGF_{2\alpha}$ and the biologically active PGI_1 (maximally in about a 2 : 3 ratio) were found as main products. Moreover the method can be extended to other iodinated prostaglandin compounds.

It can be concluded that the stereochemistry of $PGF_{2\alpha}$ formation by the electrochemical reduction of its iodinated derivative on a mercury cathode gives some interesting information about the stereochemical processes, since the enhancement of the 5-E isomer ratio was the outcome of the electrochemical process.

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