TECHNICAL NOTE

Nickel-catalysed electrosynthesis of anti-inflammatory agents. III. A new electrolyser for organic solvents; oxidation of metal powder as an alternative to sacrificial anodes

J. F. FAUVARQUE*, Y. DE ZELICOURT

Laboratoire de Marcoussis, Route de Nozay, F 91460 Marcoussis, France

C. AMATORE, A, JUTAND

Laboratoire de Chimie, Ecole Normale Supérieure, UA 1110, 24 Rue Lhomond, F 75231 Paris Cedex 5, France

1. Introduction

The nickel-catalysed electrosynthesis of aryl-2-propionic acids, which are anti-inflammatory agents, has been performed in an undivided cell, by electrolysing with a constant current, on a scale of 50 mmol in 100 ml of solvent [1–3]. In this process, oxidation of lithium oxalate was the anodic reaction. The anode and the cathode were two plates with a constant distance between them so that the voltage and the ohmic drop were almost constant during the electrolysis.

Other procedures using sacrificial anodes have also been described [4, 5]. When the sacrificial anodes are metal rods, they dissolve during the electrolysis and the distance between the anode and the cathode is not constant, becoming larger with time. The ohmic drop and, consequently, the Joule-heating effect increase during the electrolysis and this may be critical for industrial purposes.

We report here results concerning electrosyntheses of aryl-2-propionic acids conducted in a new type of electrolyser in which the ohmic drop has been minimized and which permits the use of a metal powder as an alternative to a sacrificial anode.

2. Experimental details

Electrolyses were carried out using a stabilized power supply (Sodilec PB Autorange). HPLC analyses were performed on a LKB apparatus with UV detector set at 254 nm, equipped with a reverse phase column (RP 8, 10 μm, 250 × 4 mm) [6]. Solvents and starting materials were purified or synthesized as previously published [3].

A new electrolyser has been built for electrosyntheses carried out in organic solvents [7]. The cell is described in Fig. 1. The electrodes [7] are described in Fig. 2. The cell was charged with 100 ml of solvent containing 0.04 M nBu$_4$NBF$_4$ as supporting electrolyte. The solution was saturated by bubbling carbon dioxide. The starting halide (50 mmol) was added to the cell followed by the catalyst (1 mmol), NiCl$_2$(PPh$_2$CH$_2$CH$_2$CH$_2$PPh$_2$), COD (1,5-cyclooctadiene) (1 mmol) and lithium oxalate or zinc powder

(70 mmol). After cooling the cell to 0° C, the electrolysis was conducted at constant current. After usual work-up [3], the products were isolated and characterized [3]. Monitoring of the electrolyses was performed by HPLC analysis [6]. Electrolyses were also carried out in 1.5 and 20 l reactors [8].

The main problem of organic solvents is their high resistivity and consequently the high Joule heating effect. To decrease these effects, it is necessary to position the electrodes as close as possible to minimize the ohmic drop. Thus the electrodes (Fig. 2) were made of two concentric conducting cylinders isolated by a very thin isolating separator. The system was held tight so that the distance between the two electrodes was the thickness of the separator (2 mm). The electrodes and the separator were porous to permit good diffusion of the ions between them. The anode and the cathode were interchangeable. When the electrolyses were conducted with zinc powder, it was better to have the anode outside (position 1 in Fig. 2) to obtain a good contact between the anode and the zinc powder. In every case, it was better to use a titanium mesh for the anode instead of nickel foam, since corrosion was significant at the nickel anode. No corrosion was observed at the nickel cathode.

3. Results and discussion

The 100 ml electrolyser was tested for the electrosynthesis of anti-inflammatory reagents, fenoprofen (m-PhO–Ph–CH(CH$_3$)CO$_2$H) and ibuprofen (p-iBu–Ph–CH(CH$_3$)CO$_2$H), according to the reaction [2, 3]

$$ArCH(CH_3)Cl + CO_2 + 2e^-$$

$$\xrightarrow[2\%]{NiCl_2(dppe)\ +\ COD} ArCH(CH_3)CO_2^- + Cl^-$$
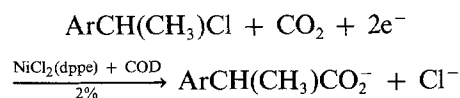
with two different anodic reactions.

3.1. *Oxidation of lithium oxalate as the anodic reaction*

The electrosyntheses of fenoprofen and ibuprofen in this new electrolyser, B, (concentric electrodes) are compared in Table 1 with results obtained with a

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* Author to whom correspondence should be addressed.

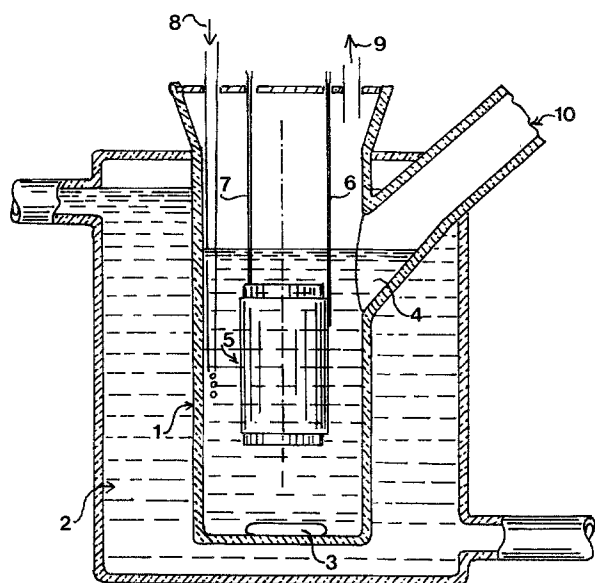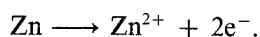Fig. 1. Electrolysis cell: 1 cell; 2 cooling liquid; 3 magnetic stirrer; 4 solution to be electrolysed (100 ml); 5 electrodes; 6 cathode; 7 anode; 8 CO_2 inlet; 9 CO_2 exit; 10 reference electrode (Ag/AgClO$_4$ 0.1 M THF).

Fig. 2. Electrodes: 1 nickel foam or titanium mesh ($S = 39\,\text{cm}^2$); 2 current input; 3 graphite woven (TMG 285, Carbone Lorraine); 4 separator, glass fibre; 5 graphite woven; 6 nickel foam or titanium mesh ($S = 17\,\text{cm}^2$); 7 current input. The distance between 3 and 5 is 2 mm.

classical electrolyser, A, in which the anode and the cathode were two rectangular plates as previously described [3].

Fenoprofen and ibuprofen were synthesized in good yields in this special electrolyser, B. The electrodes are so close that the voltage between them is smaller by a factor of four, compared with the classical system, A, for the same value of the current (compare the values of V in entries 1 and 2, 3 and 4, and 5 and 6 in Table 1). The voltage was constant during the electrolysis.

3.2. Oxidation of metal powder as the anodic reaction

Instead of lithium oxalate it was possible to use metal powder (zinc or magnesium) which was oxidized on coming into contact with the anode

$$Zn \longrightarrow Zn^{2+} + 2e^-.$$

Fenoprofen was synthesized in good yield in this new electrolyser using oxidation of a metal powder as the anodic reaction. First, we have checked that no
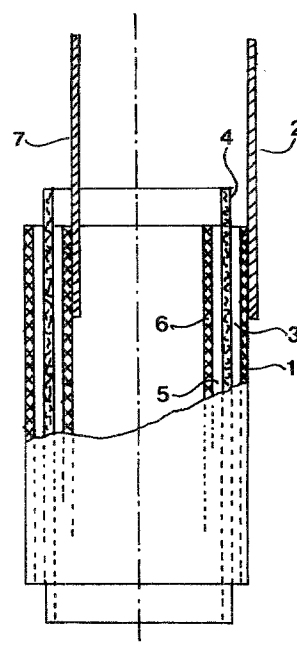
reaction occurred without electrolysis. Neither Zn powder nor Mg turnings reacted with the starting halide under the experimental conditions (2° C, TMU as solvent). The voltage between the anode and the cathode was constant except at the very end of electrolysis, which demonstrates that this electrolyser is versatile; it can work successfully with metal powder which dissolves by oxidation at the anode. Best results were obtained with zinc powder (entry 7) and were similar to those obtained with lithium oxalate (entry 4). Figure 3 shows the progress of the electrosyntheses of fenoprofen in the presence of zinc powder as a function of the charge passed through the cell. Moreover, if the electrolysis is interrupted after an appreciable charge has passed (ca. 5000 to 10 000 C), the reaction does not proceed, which shows that the role of the Zn powder is essentially that of an anodic reagent and that it does not act as homogeneous chemical reagent even after anodic surface activation.

Table 1. Comparison of electrosyntheses of fenoprofen and ibuprofen in two different cell arrangements

	$ArCH(CH_3)CO_2H$		Solvent	$I\,(mA)$	V (V)	$(F\,mol^{-1})$	$ArCH(CH_3)CO_2H$			RH (%)
							τ (%)	R_c (%)	R_F (%)	
1	Fenoprofen	A	THF + HMPA	400	35	2.6	83	69	44	–
2		B	THF + HMPA	400	9	2.6	76	80	46	3
3		A	TMU	400	23	2.6	78	82	49	3.5
4		B	TMU	600	9.5	2.5	80	85	54	1.4
5	Ibuprofen	A	TMU	400	23	3	83	62	34	–
6		B	TMU	600	9	2.5	77	69	35	3.5

A Plate electrodes [3]; B Concentric electrodes. $T = 0°\,C$; $P_{CO_2} = 1\,\text{atm}$; [ArCH(CH$_3$)Cl] = 50 mmol; [Li$_2$C$_2$O$_4$] = 70 mmol; [NiCl$_2$ (dppp)] = 1 mmol; [COD] = 1 mmol; Solvent 100 ml; TMU, tetramethylurea. Mixture of THF + HMPA (hexamethylphosphorotriamide): 2 + 1 in volume. V, voltage between the anode and the cathode. (F mol^{-1}) refer to the starting halide. τ is the conversion rate. R_c is the chemical yield (determined by HPLC). R_F is the current efficiency. RH is m-PhO–Ph–CH$_2$CH$_3$ for fenoprofen or p-iBu–Ph–CH$_2$CH$_3$ for ibuprofen.
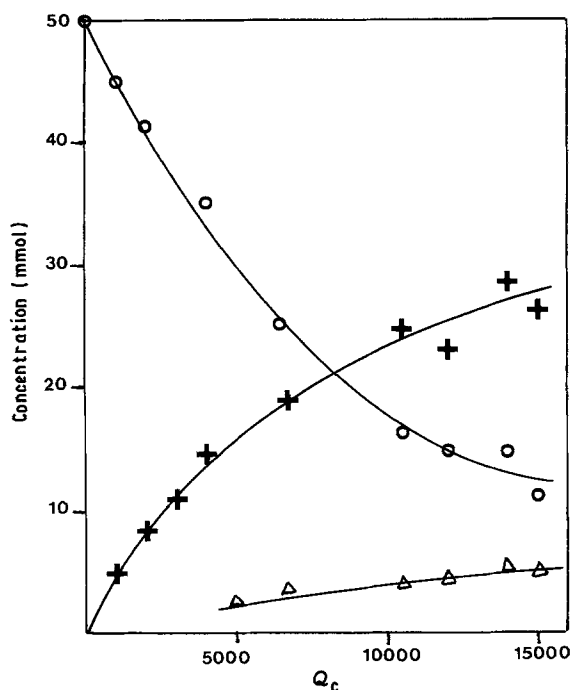
Fig. 3. Electrosynthesis of fenoprofen (R = m-PhO-Ph-CH(CH₃)-):
○ RCe, + RCO₂H, △ RH. [m-PhO-Ph-CH(CH₃)Cl] = 50 mmol;
[Zn] = 70 mmol; [NiCl₂(dppp)] = 1 mmol; [COD] = 1 mmol.
Solvent: TMU, 100 ml. $T = 2°C$. $P_{CO_2} = 1$ atm. $I = 600$ mA.
Cathode: nickel foam + graphite woven. Anode: titanium mesh +
graphite woven. HPLC analysis [6]: eluant CH₃CN (48%) and H₂O
(52%) containing 2 vol % acetic acid; flow rate: 1 ml min⁻¹.

In addition, we checked that no electrodeposition of
zinc occurred on the cathode which can be easily
explained by the formation of a stable zinc carboxylate
as the product reaction. Moreover the latter is not
electroreducible under our experimental conditions.
This is in agreement with the close identity of the
current efficiency (column labelled R_F in Table 2) for
oxidation of zinc powder and lithium oxalate (entry 4
and 7).

4. Conclusion

Nickel catalysed electrosyntheses of ibuprofen and
fenoprofen, which are anti-inflammatory reagents,
have been performed with good yields in a special type
of electrolyser, an undivided cell with concentric elec-
trodes held as close as possible to minimize the ohmic
drop, thus allowing the use of resistive organic sol-

Table 2. Electrolysis with oxidation of metal powder using concentric
electrodes, B

Anodic reaction	I (mA)	V (V)	Fenoprofen			RH (%)
			τ (%)	R_c (%)	R_F (%)	
4 Li₂C₂O₄	600	9.5	80	85	44	1.4
7 Zn (powder)	600	9	77	88	43	4.7
8 Mg (turnings)	600	9	52	96	37	–

Experimental conditions were the same as in Table 1, B. Solvent:
TMU. [Metal powder] = 70 mmol.

vents. The electrolyses can be carried out galvanostat-
ically with a constant voltage between the anode and
the cathode. This electrolyser can operate under
heterogeneous conditions (in the present case, lithium
oxalate or metal powder in suspension with a gas
bubbling in the solution). Zinc powder, added to the
solution, can be easily oxidized when contacting the
anode. This is a good alternative to the use of sacri-
ficial anodes.

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