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Nickel catalysed electrosynthesis of anti-inflammatory agents. Part II – Monitoring of the electrolyses by HPLC analysis. Role of the catalyst

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A method of analysis has been developed by HPLC to monitor the progress of the electrosynthesis of aryl-2 propionic acids. This method elucidates the role of the nickel catalyst.

1. Introduction

We recently developed a new electrosynthesis of aryl-2 propionic acids which are anti-inflammatory agents [1–3] according to the reaction:

$$ArCH(CH_3)Cl + CO_2 + 2e^- \xrightarrow{Ni^{II}} ArCH(CH_3)COO^- + Cl^-$$

The catalyst was $NiCl_2$ (dppp) (dppp = PPh_2CH_2-$CH_2CH_2PPh_2$), associated to one equivalent of a labile coligand COD (1,5-cyclo-octadiene). The electrolyses were conducted in an undivided cell with a constant current using concentrated solutions (0.5 M) with or without a catalyst. $Li_2C_2O_4$, which was added to the cell, was oxidized at the anode. Two anti-inflammatory agents were synthesized, fenoprofen and ibuprofen with a conversion rate superior to 75% and chemical yield close to 85% [3].

When carrying out systematic electrolyses in order to optimize these reactions, we attempted to develop a convenient method of analysing the solutions at the end or during the electrolyses without isolating the products and reagents. Analytical HPLC proved to be a successful method.

2. Results and discussion

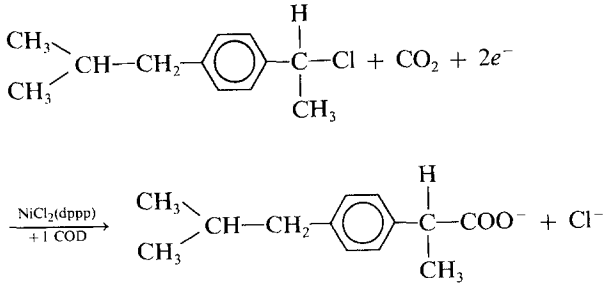
2.1. *Analytical procedure*

HPLC analyses were performed on a LKB apparatus. Since the solutions to be analysed contained polar compounds such as the supporting electrolyte nBu_4NBF_4, the aryl-2 propionic acid synthesized as a lithium carboxylate, and lithium oxalate, we used a reverse phase column (RP8, 10 μm, 250 × 4 mm). The eluant was a mixture of acetonitrile and water containing 2% by weight of acetic acid in which the products were readily soluble. Very polar compounds such as aryl-2 propionic acid, lithium oxalate and nBu_4NBF_4 were eluted first, followed by less polar compounds such as $ArCH(CH_3)Cl$. The HPLC was equipped with an ultraviolet detector set at 254 nm, which permits the detection of aromatic molecules. This analytical method is particularly suitable for the analysis of electrolyses since solutions always contain a supporting electrolyte which will be eluted first without any UV absorption. Since the solvents employed, such as HMPA or TMU (tetramethylurea), have very small absorption at 254 nm, only the products and reagents of these electrosyntheses were detected.

Every product and reagent of the reaction was injected separately into the HPLC system and characterized by its retention time and UV response relative to an internal standard.

At the end of the electrolysis, a known amount of an internal standard was added to the solution. A sample of 100 μl was withdrawn from the solution and diluted (× 200) with a mixture of acetonitrile and water containing 2% of acetic acid. The diluted sample (20 μl) was directly injected into the HPLC system.

A typical chromatogram is shown in Fig. 1. The analysed solution resulted from the electrosynthesis of ibuprofen according to the reaction:



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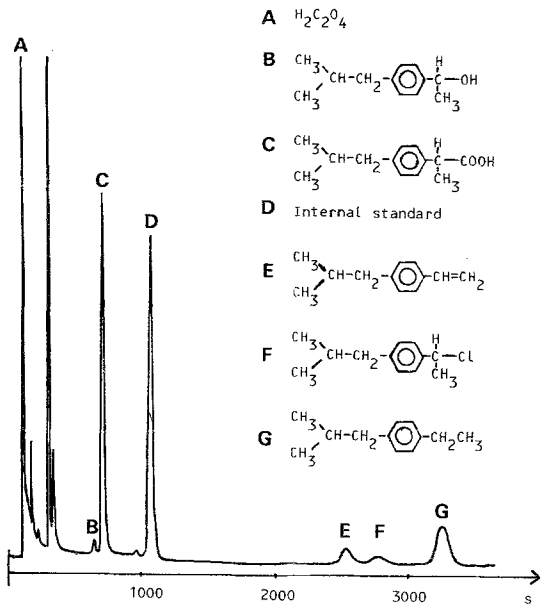


Fig. 1. HPLC chromatogram of an electrosynthesis of ibuprofen. Internal standard: $PhCH_2OCH_2Ph$. *Eluant* = CH_3CN + H_2O (48% + 52%); *Flow rate* = 1 ml mn^{-1}.

The electrolysis was conducted in an undivided cell as previously described [3], on 50 mmol of *p-i*Bu-Ph-$CH(CH_3)Cl$ in 100 ml of TMU containing nBu_4NBF_4 0.04 M, at 0° C, under atmospheric pressure of carbon dioxide, in the presence of 1 mmol of the catalyst $NiCl_2$(dppp) + COD and 70 mmol of $Li_2C_2O_4$. The current was fixed at 400 mA (2 A dm^{-2}). The electrolysis was stopped after 3 Faradays per mol of *p-i*Bu-Ph-$CH(CH_3)Cl$ had been passed.

We checked that results obtained with HPLC analyses were similar to those obtained with isolated products [3]. *P-i*Bu-Ph-CH_2CH_3 was detected more precisely by HPLC analysis.

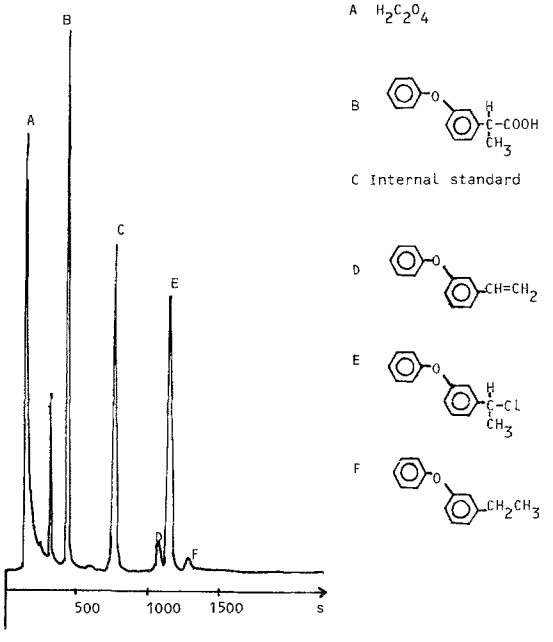
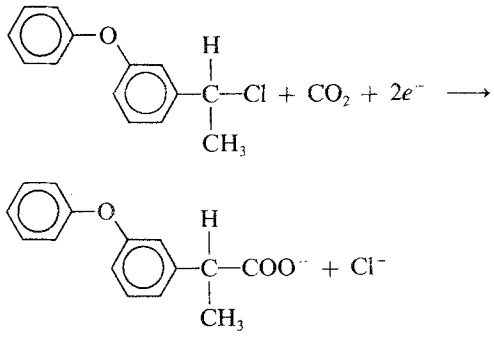


Fig. 2. HPLC chromatogram of an electrosynthesis of fenoprofen. Internal standard: $PhCH_2OCH_2Ph$. *Eluant* = CH_3CN + H_2O (55% + 45%); *Flow rate* = 0.8 ml mn^{-1}.

2.2. *Monitoring of the electrolyses by HPLC analysis*

This analytical method by HPLC is very convenient for the analysis of the reaction mixture during the electrolysis and enables, at any time, the determination of the amount of acid and halide present in the solution without isolating them. We report here the evolution of the electrosynthetic medium for the electrosynthesis of fenoprofen with and without nickel catalyst.



2.2.1. Evolution of the electrosyntheses without catalyst. The electrolysis was conducted under the same experimental conditions as for the electrosynthesis of ibuprofen (50 mmol of *m*PhO-Ph-$CH(CH_3)Cl$, I = 500 mA). Fig. 2 shows a chromatogram obtained for the analysis of one sample withdrawn from the solution after 2 F mol^{-1} had been passed through the cell. The suitable amount of the internal standard was added to the sample.

Fig. 3 shows the relative formation of fenoprofen and disappearance of *m*PhO-Ph-$CH(CH_3)Cl$ as a function of the charge passed through the cell. Samples of 100 μl were withdrawn from the solution every 1000 Coulombs and analysed by HPLC.

In the case of the following reaction: $RX + CO_2 + 2e^- \rightarrow RCO_2^- + X^-$, carried out without catalyst

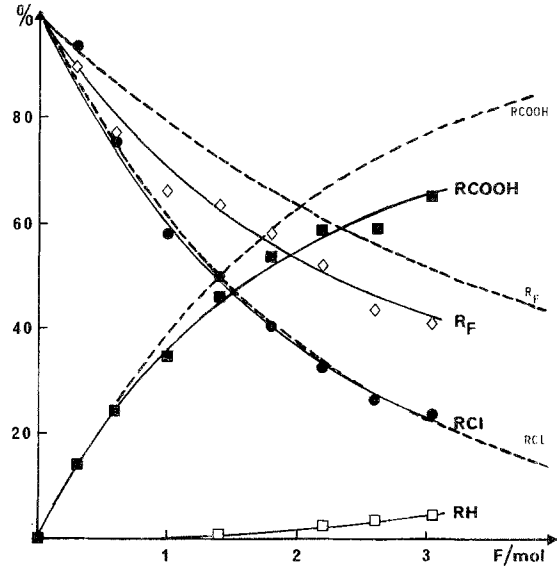


Fig. 3. Evolution of the electrosynthesis of fenoprofen without catalyst. RCOOH = fenoprofen; RCl = *m*PhO-Ph-$CH(CH_3)Cl$; RH = *m*PhO-Ph-CH_2CH_3; $Li_2C_2O_4$ = 70 mmol; *Cathode*: nickel foam; *Anode*: graphite; I = 500 mA (2.5 A dm^{-2}); R_F = current efficiency. (– – –) theoretical curves; (——) experimental curves.

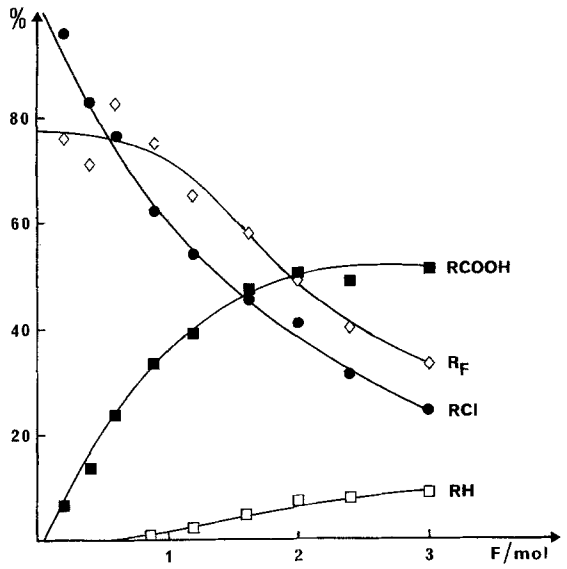


Fig. 4. Evolution of the electrosynthesis of fenoprofen with a nickel catalyst. RCOOH = fenoprofen; RCl = *m*PhO-Ph-CH(CH_3)Cl; RH = *m*PhO-Ph-CH_2CH_3; $Li_2C_2O_4$ = 70 mmol; *Cathode*: nickel foam; *Anode*: graphite. I = 750 mA (3.75 A dm^{-2}). R_F = current efficiency.

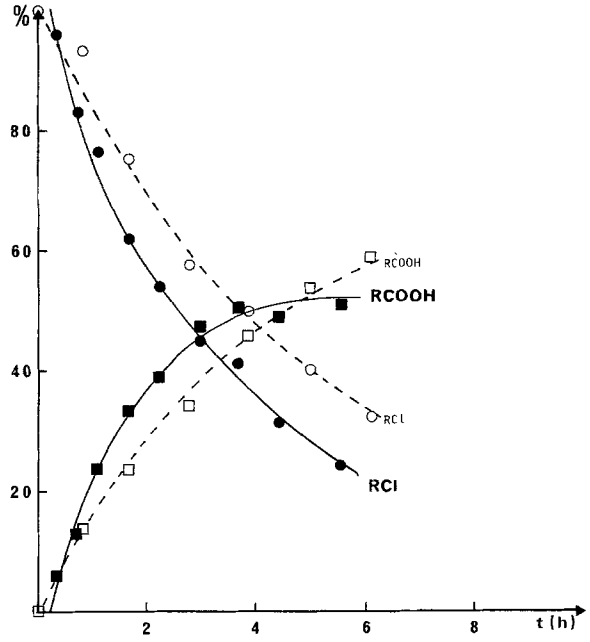


Fig. 5. (□ ○) electrosynthesis of fenoprofen without catalyst, I = 500 mA. (■ ●) electrosynthesis of fenoprofen with catalyst, $NiCl_2$(dppp) + COD, I = 750 mA.

and with a constant current, it is possible to calculate the amount of the acid which is formed and the amount of RX still present in the solution as a function of the charge.

If I is the limiting current, the disappearance of RX should follow the relation: $n = n_0 e\,(-It/nNF)$ where n_0 = mmol of RX at $t = 0$; n = mmol of RX at t; N = number of electrons per mol ($N = 2$); $F = 96500\,C\,mol^{-1}$.

If RCO_2H is the only product formed by the reaction, we can calculate the formation of RCO_2H and the current efficiency R_F as a function of the charge passed through the cell. Theoretical curves are presented on Fig. 3 by the dashed lines and compared to experimental curves obtained during the electrosynthesis of fenoprofen.

The curve representing the disappearance of *m*PhO-Ph-CH(CH_3)Cl is similar to the theoretical curve. This means perhaps that the value of the current (I = 500 mA) chosen for the electrosynthesis of fenoprofen is close to the limiting current at the beginning of the electrolysis.

The curve representing the rate of formation of fenoprofen is below the theoretical curve, because of the formation of a by-product, *m*PhO-Ph-CH_2CH_3 and so the current efficiency is always inferior to the theoretical one.

2.2.2. Progress of the electrosyntheses with a catalyst. The electrolysis was conducted on 50 mmol of *m*PhO-Ph-CH(CH_3)Cl in the presence of 1 mmol of $NiCl_2$ (dppp) and 1 mmol of COD. The current was 750 mA. Fig. 4 represents the rate of formation of fenoprofen and disappearance of the starting halide as a function of the charge passed through the cell.

2.2.3. Role of the catalyst. When the electrolysis is performed in the presence of a catalyst, it can be seen from the Fig. 4, that the current efficiency is constant until one Faraday per mol has been passed through the cell. During this period, the electrolysis probably proceeds through the reduction of the insertion complex, *m*PhO-Ph-CH(CH_3)NiCl(dppp) which is the suggested intermediate continually recycled during such reaction [2]. The current efficiency is not as good as in a divided cell [2] probably because of the reoxidation of the nickel catalyst at the anode.

Fig. 5 shows the results of electrolyses with and without catalyst as a function of time.

Clearly the reaction proceeds faster at the beginning when the catalyst is present. 47% of fenoprofen was obtained after 3 h in the presence of the catalyst and only 37% without catalyst.

With a catalyst, we can apply a higher current (750 mA instead of 500 mA for the same cathodic potential). But with 750 mA, at the end of the electrolysis, overheating of the medium avoids efficient catalysis of the reaction by deactivation of the catalyst or by diminution of carbon dioxide solubility, thus, reduction of the starting chloride is favoured over electrocarboxylation. The applied current should be decreased at the end of the electrolysis in order to maintain a good catalytic activity with a constant current efficiency.

3. Conclusion

HPLC is a very convenient method for analysing electrochemical syntheses. The direct injection into the HPLC system of samples withdrawn from the solution permits the identification and quantification of the products and reagents at the end of, or during the electrolyses. The analysis of the evolution of the electrosyntheses enables a better understanding of the role of the nickel catalyst.

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