JOURNAL OF APPLIED ELECTROCHEMISTRY **28** (1998) 569–577

Process development for electrocarboxylation of 2-acetyl-6-methoxynaphthalene

A. K. DATTA, P. A. MARRON
Searle, 5200 Old Orchard Rd., Skokie, IL 60077, USA

C. J. H. KING
Monsanto Co., 3000 Old Chemstrand Rd, Cantonment, FL 32533, USA

J. H. WAGENKNECHT*
Cedar Hill LLC, 7510 Horseplay Lane, Cedar Hill, MO 63016, USA

Received 25 June 1997; revised 28 October 1997

Electrochemical carboxylation of 2-acetyl-6-methoxynaphthalene to 2-hydroxy-2-(6-methoxy-2-naphthyl)propionic acid may be carried out in good yield (~89% in the electrolysis; 75% as isolated dried product) in an undivided flow cell using lead as the cathode and aluminium as the dissolving anode. Dimethylformamide was found to be the best solvent for the reaction and low cost tetraethylammonium chloride hydrate is a good electrolyte for the system. The best conditions are those that increase carbon dioxide concentration although higher pressure seems to be more effective than low temperature. The reaction may be carried out with good yield at fairly high current density ($1150\,\mathrm{A\,m^{-1}}$) and higher current densities are likely attainable. The allowable payload is limited to around 10% because higher payloads (20%) resulted in solution too viscous to pump. Initially it was surmised that trace quantities of water would be detrimental to good yields in these reactions. However, it was found that small amounts of water (that associated with typical quaternary ammonium chloride salts) has the beneficial effect of eliminating the major byproduct which is formed in more nearly anhydrous solutions without resulting in formation of alternative byproducts. Process conditions were evaluated at 0.2 L scale, then scaled up to 1 L and finally 75 L. The best results were attained in the 1 L system, solvable operating problems limited the yield in the largest scale electrolysis.

Keywords: *electrocarboxylation*, *sacrifical anode*, *naproxen*, *process development*, *pilot plant*

1. Introduction

New nonsteriodal antiinflammatory drugs (NSAIDs) such as ibuprofen and naproxen are now available in nonprescription form. These drugs as well as related prescription NSAIDs have a common structural feature in that they are 2-arylpropionic acids (or salts). A new synthetic scheme for production of these NSAIDs was discovered several years ago [1–4]. Initial work was aimed at a process for ibuprofen which does not require a single chiral isomer. Later, catalysts were discovered for chiral hydrogenation of dehydronaproxen to S-naproxen [5]. This led to further unpublished development of the electrochemical step and product isolation procedures by Chan, Powers and King at Monsanto and Kim at Searle [6]. This paper describes work aimed at improving the electrochemical carboxylation step in terms of yield and mode of operation so that confident estimates of the cost of a commercial process could be made.

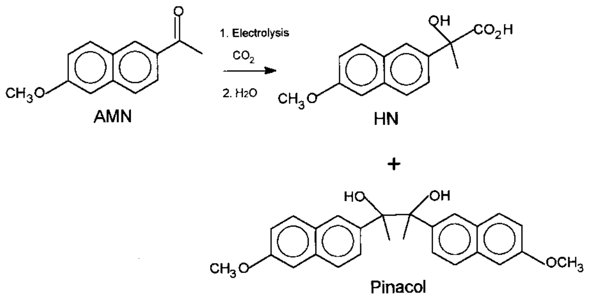
The chemical structures and reaction sequences which are the subject of this study are shown in Scheme 1. The raw material for the reaction is 2-acetyl-6-methoxynaphthalene (AMN) and the desired product is 2-hydroxy-2-(6-methoxy-2-naphthyl)propionic acid (HN) (for hydroxynaproxen). A common byproduct is formed by dimerization with coupling at the carbonyl carbon and in this report that product will be referred to as 'pinacol'.

The earliest report of electrocarboxylation of an arylketone was by Wawzonek [7] who reported a low yield of carboxylated product from acetophenone. That was confirmed later by Hori *et al.* [8], and later yet by Engels *et al.* [9] who found that acetophenone could be electrochemically carboxylated in good yield in an undivided cell using an oxalate electrolyte. The early work involving electrocarboxylation of an arylketone leading to an intermediate for a NSAID (ibuprofen) was done around the same time in Japan [1] and the USA [2, 3].

---

* Author to whom correspondence should be addressed.

0021-891X



Scheme 1

In prior work at Monsanto the electrochemical carboxylation of AMN had been carried out in an undivided electrochemical cell in dimethylformamide (DMF) as the solvent with tetrabutylammonium bromide as the supporting electrolyte [6]. The cathode used was lead and the anode was aluminium. In this process the desired carboxylation reaction occurs at the cathode and at the anode aluminium metal is oxidized to aluminium ion.

The dissolving anode scheme for performing electrochemical carboxylations in undivided cells has been well developed by Silvestri and coworkers including development of a process for electrocarboxylation of AMN using a sacrifical anode process. Silvestri *et al.* have published excellent exhaustive review articles covering work in sacrificial anodes [10, 11]. Tomilov [12] and Tokuda [13] have published more recent reviews of the area. Chaussard recently reported on a pilot plant electrocarboxylation [14]. Perichon has been active in the area of electrocarboxylations involving sacrifical anodes, and references to that work may be found in [15–18]. Recent publications related to this area by Torii [19] and Zheng [20] are included as key sources of recent references. A very interesting history of the process chemistry for naproxen at Syntex was published recently [21].

2. Experimental details

Purified samples of AMN, HN and pinacol were obtained from Searle and used for HPLC standards. Large supplies of AMN were obtained from Riverside Chemical Co. (300 Tower, Renaissance Center, Detroit, MI). Dimethylformamide (DMF) used for the electrolysis solvent was Aldrich special anhydrous grade and DMF used for rinsing the electrolysis system was Fisher reagent grade. The initial plan was to use anhydrous carbon dioxide but delivery problems resulted in use of low-cost welding-grade carbon dioxide. It was later discovered that traces of water are not detrimental to the reaction, so the high cost anhydrous material was not required. Acetonitrile used as electrolysis solvent was HPLC grade. *N*-methylpyrrolidinone used for an electrolysis solvent was Aldrich anhydrous grade. Tetrabutylammonium bromide, tetrabutylammonium tetrafluoroborate, tetraethylammonium bromide, and tetraethylammonium chloride were all from Aldrich and used as received. Aluminium plate used for anodes was cut from scrap aluminium sheet obtained from the shop. Pure lead electrodes were from stocks of unknown origin. A sample of lead-plated mild steel was obtained from Verichrome Plating Services Ltd, (Larkhall, Lanarkshire, Scotland) and cut to fit the cell. The back side of one of those electrodes served as a mild steel cathode. Stainless-steel (SS) cathode was cut from a piece of scrap 304 SS sheet from the shop. Graphite sheet and zinc sheet used for cathodes were obtained from stock, origin unknown.

Voltammetry was carried out using a Princeton Applied Research potentiostat/galvanostat (model 273A) controlled by an Ultra-Comp 386/33 computer (PAR model 270) running electrochemical analysis software version 3.00. Output was to a Hewlett-Packard (7550A) plotter. The voltammetry cell was a PAR clamp-on small-volume cell with a platinum coil counter electrode, Van London Ag/AgCl reference electrode and IBM glassy carbon working electrode. Solutions were degassed and stirred using house nitrogen. Fisher reagent DMF was used to make up solutions.

2.1. *Analysis*

The HPLC system consisted of a Varian 9010 pump station, a Varian 9095 autosampler, a 150 × 4.6 mm Keystone Scientific, Inc. ODS-Hypersil column (C18 type, particle size 3 μm, pore size 120 Å) contained in a Flatron CH-30 column heater (kept at room temperature), a Varian 9065 diode-array u.v. detector and a Hewlitt-Packard Vectra Q5/20 computer. Varian Star software controlled the system.

Mobile phase A was 35% acetonitrile, 64% water and 1% acetic acid. Mobile phase B was 55% acetonitrile, 44% water and 1% acetic acid. The mobile-phase solutions were prepared from HPLC-grade reagents and filtered through a 0.45 μm filter before use. The elution program began with mobile phase A for 10 min, then over the next 10 min, a linear conversion to mobile phase B followed by 20 min of mobile phase B all pumping at 1.0 mL min^{-1}. The elution times for the various components are about 6 min for HN, 20 min for AMN and 27 and 28 min for pinacol. The major common unknown elutes around 10 min.

2.2. *Small-scale (200 mL) electrolysis system*

The system was a recirculating solution design. Starting with the pump (Micropump model 101–415; magnetic drive centrifugal with SS head) the flow proceeds via 0.635 cm polyethylene tubing to a heat exchanger coil (a 61 cm length of 0.635 cm o.d. stainless steel tubing having a five turn coil of diameter 4.45 cm). The heat exchanger coil fit into the bath of a Lauda K-2/R refrigeration unit containing 50% automotive antifreeze. The Lauda unit was coupled via flow of the antifreeze solution through a coil to a Tamson 19 L bath (also containing 50% automotive antifreeze) cooled by a Neslab PBC-2 refrigeration unit. After exiting the heat exchanger coil, the electrolysis solution proceeded via 0.635 cm OD polyethylene tubing to the cell. Details of the cell will be described separately. After leaving the cell, the flow proceeded via 0.635 cm o.d. polyethylene tubing to a 0.635 cm SS tubing cross fitting. Also attached to the cross fitting were a ball valve used for liquid filling and gas venting of the system and another line leading to a SS tee with a 0 to 690 kPa gauge and continuing to a check valve and the carbon dioxide supply line (0.317 cm o.d. Teflon tubing). After leaving the SS cross, the electrolysis solution passed via SS fittings into a 100 mL SS reservoir flowing then via 0.635 cm OD polyethylene tubing to a SS tee, then to another SS tee and finally returning via 0.635 cm SS tubing to the intake of the pump. The first tee after the reservoir had within it a K-type thermocouple connected via appropriate SS fittings. The thermocouple was monitored with an Omega (model 199) digital display unit. The second tee branched to a ball valve which was the lowest point in the system and was used to drain the system and to collect samples during an experiment.

2.3. *Small electrolysis cell*

The small electrolysis cell was of typical plate and frame design with 0.315 cm thick steel backing plates. The cathode was lead sheet or lead-plated steel and the anode was 1.6 mm thick aluminium sheet. The electrode separator was a 1 mm thick Teflon sheet which had a 20 cm^2 flow channel cut out of it. The anode was insulated from the backing plate by a 0.635 cm polyethylene sheet. Solution inlet and outlet was via fittings and holes in the anode, polyethylene and backplate. The assembly was held together by 10 bolts and nuts. On assembly of the parts the contacting surfaces between cathode and Teflon spacer, Teflon spacer and anode and anode and polyethylene back plate were coated with a thin coat of silicone rubber cement (Dow Corning 742 RTV clear sealant). Electrical power to the cell was supplied by a Sorenson DCR80-6B constant-current power supply.

2.4. *Operation of the 200 mL system*

For the typical experiment, the cell was assembled using a new aluminium anode at least overnight before an experiment in order for the silicone rubber cement to cure. The solution (typically 7.7 g tetrabutylammonium bromide, 20 g of AMN and 180 mL of anhydrous DMF) was prepared in a sealed bottle and transferred to the cell using a glass 50 mL syringe and injecting into the electrolysis cell end of the tubing connecting the heat exchanger and cell. Then the pump was started and the system was twice pressurized with carbon dioxide to about 70 kPa and vented via the ball valve at the top. Finally, the unit was pressurized to 138 kPa with carbon dioxide. When the temperature reached the desired point (typically 20 °C) the power supply to the cell was switched on (typically at 2 A controlled current). A small liquid sample (~1 mL) was obtained at the lower ball valve at the beginning and at several intervals during a run. During the typical run, the solution initially became bright yellow but later this colour was masked by a dark material which is presumed to be colloidal aluminium. Also during a typical run, the cell voltage increased from ~6 to ~12 V. At the end of a run, the system was drained at the bottom ball valve and residual solution blown out using house nitrogen. Two 150 mL portions of reagent DMF were used to rinse the system and these were added to the product for workup. The cell was generally immediately opened, examined (typically 0.5 mm of the aluminium exposed to the electrolysis had been evenly removed) and reassembled using a new anode for the next run.

After the electrolysis the solution was distilled at reduced pressure (pot temperature approximately 45 °C) to remove most of the DMF. To the well stirred residue was added slowly 200 mL water followed by a solution consisting of 25 mL of concentrated HCl and 35 mL of water. The resulting slurry was stirred for 0.5 h and vacuum filtered. The crude solid was dried under vacuum (17 kPa) overnight.

2.5. *1 L electrolysis system*

The system is similar to the smaller one. Starting at the pump (Micropump model 101-415) the flow proceeds via 0.95 cm SS tubing to the cell (described below), then via 0.95 cm polypropylene tubing to a 0.95 cm SS cross fitting. The cross fitting has a ball valve for venting mounted on top and is connected to the carbon dioxide supply via a tee holding a 0 to 690 kPa pressure gauge and check valve. The flow of electrolysis solution proceeds from the cross to a 1 L SS reservoir and then through a heat exchanger (0.95 cm SS tubing coiled in a 3.8 L can filled with antifreeze), past two SS tees and returning to the pump. The first tee contains a K-type thermocouple mounted with SS fittings and the second tee has a ball valve for draining on the branch. The cell was powered by two Sorenson DCR80-6B power supplies wired in parallel. The power supplies maximum current were 6.85 A and 7.53 A for a combined current of 14.38 A. That represents a current density of 1130 A m^{-2} at the 127.5 cm^2 cathode area in the cell.

2.6. *Operation of the 1 L system*

The system was filled with a mixture consisting of 100 g AMN, 20 g of tetraethylammonium chloride and 900 mL of anhydrous DMF by connecting a vacuum to the top valve and drawing the solution in through the lower valve. The system was pressurized to 138 kPa with carbon dioxide, circulated and vented twice to remove air and then pressurized to 690 kPa with carbon dioxide while the solution was pumped around in the system. The translucent polypropylene tubing at the top of the system allowed visual observation of solution flow. Both power supplies were turned on to maximum current (6.85 and 7.53 A). Dry ice was added manually to the antifreeze solution in the cooling can to maintain the temperature of the circulating solution at 20 °C. Samples were removed at the beginning and at 40 min intervals for analysis. The electrolysis was stopped at 2 h 20 min. The system was drained and washed with two 1 L portions of reagent DMF. The combined solutions were subjected to the workup procedure indicated above.

The cell used for the 1 L experiments was a plate-and-frame cell with heavy fibre glass–epoxy end plates, sheet aluminium and lead–steel electrodes separated by a rubber gasket with flow channel cut out. The flow channel was 2.54 cm wide by 50 cm long. Flow inlet and outlet were via channels machined into the polyethylene plates which were positioned between electrodes and end plates.

2.7. *75 L system*

The electrolysis unit, schematically depicted in Figure 1, consisted of a 115 L jacketed (cooled with chilled water) vessel, pump, 100 μm cartridge filter and two plate and frame cells (3.66 m × 2.62 cm) with parallel electrolyte flow controlled by parallel flow controllers. The cells were mounted nearly horizontally (reduced head pressure compared to vertical mount) but with a small incline to the exit end to aid in draining the cells. The cells were fitted with 3.2 mm thick aluminium anodes and lead (0.05 mm thick) on steel (Verichrome Plating Services) cathodes. All operating parameters were data logged every 30 s and these readings were averaged in groups of 12. The system was charged with 8.3 kg of AMN, 3 kg of Bu_4NBr and 72 kg of DMF. The system was pressurized with CO_2 in the range from 414 to 515 kPa and the solution cooled to 20 °C. Solution flow through each cell was targeted at 1.2 m s^{-1}. The current to the cells (electrically in series) was set at 90 A (~1000 A m^{-2}) although late in the run, the current was reduced due to overheating of the rectifier. The electrolysis was operated for 24 h with some short shutdown periods to fix various problems such as leaks, instrument problems etc.

After the electrolysis most of the DMF was removed from the solution by vacuum distillation from the 115 L vessel by applying steam to the jacket. The residue was transferred to a 570 L vessel to which water and HCl were added to decompose the aluminium salt and precipitate crude HN. Crude solid HN was removed using a crock filter. The crude solid was purified by mixing with toluene, water and triethylamine, filtering, separating the organic phase (containing unreacted AMN and some byproducts), acidifying the aqueous phase to precipitate HN, recovering HN in a crock filter and drying.

3. Results and discussion

A series of electrolyses was carried out in the small 200 mL system to learn the effect of the main variables on the yield of HN produced from the electrochemical carboxylation of AMN in an undivided plate-and-frame flow cell operated under batch recirculating flow conditions. The variables included cathode material, current density, electrolyte, solvent, temperature, pressure and payload. The plan was to define a set of standard conditions and then vary only one parameter at a time in that set and then to combine the optimal set of variables to obtain the best possible yield. This was to be followed by a statistically designed set of experiments involving the important variables, but that was not done.

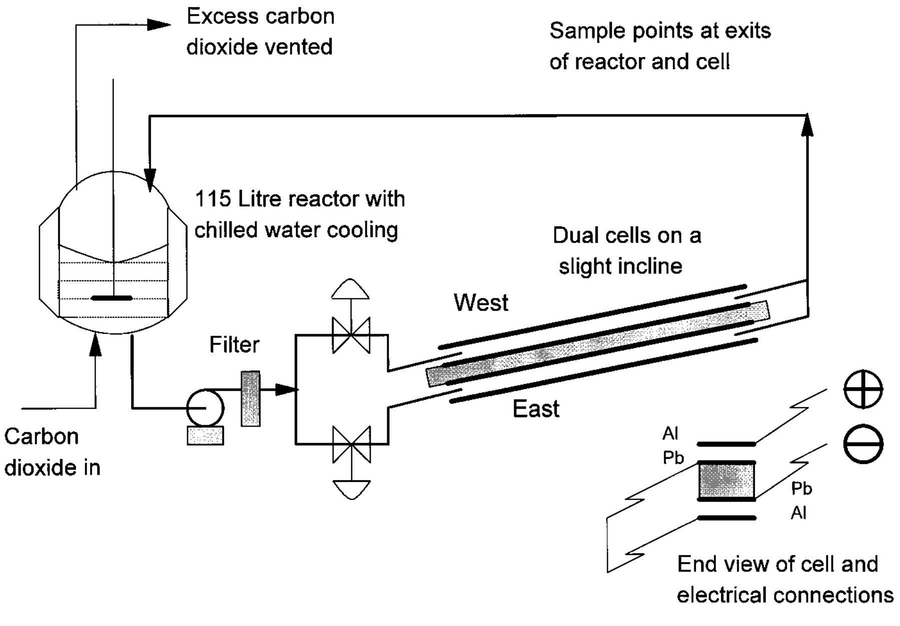


Fig. 1. Layout scheme for the 75 L electrolysis unit.

3.1. *Standard conditions*

The solution consisted of 20 g of AMN and 7.7 g of tetrabutylammonium bromide dissolved in 180 mL of DMF. The standard cathode was lead plated steel, the standard anode was aluminium. The standard carbon dioxide pressure was 138 kPa and the standard temperature 20 °C. The standard current density was 1000 A m^{-2} (2 A for the 20 cm^2, 1 mm gap cell used). Most electrolyses were run for 3.5 h. Details of the system and procedure are in Section 2.

Single variations from the standard were as follows: Cathode: zinc, mild steel, aluminium, stainless steel and graphite; electrolyte: tetraethylammonium chloride hydrate, tetraethylammonium bromide and sodium bromide; pressure 690 kPa; temperature 5 °C; current density 250 A m^{-2}; payload 20% and 5%; solvent: acetonitrile and *N*-methylpyrrolidinone.

3.2. *Standard electrolysis*

The results of the standard electrolysis and electrolyses with variation in conditions are shown in Table 1. In the Table, the results of HPLC analysis of the final electrolysis solution are listed. The standard conditions gave a molar HN yield of 66.2% at 87.65% conversion or 75% yield based on converted AMN (selectivity). The major unknown product represented a large loss in yield of HN. The yield of pinacol is about 3%. Also included in Table 1 is a column headed 'Voltage'. The numbers indicate the cell voltage at the beginning and end of a particular electrolysis.

The increase of voltage during these experiments is a result of nearly a doubling of the cell gap because of corrosion of the aluminium anode and a decrease of conductivity of the solution due to a doubling of viscosity and probably formation of large complex ions with low mobility. In some cases, very high cell voltages were observed because of buildup of solids in the cell.

Reducing the current density to 250 A m^{-2} had little effect on the yield. Note that the quantity of components was reduced to 75% of normal to shorten the time required for completion of the reaction.

3.3. *Alternative cathode materials*

The use of the alternative cathode materials led to poorer yields except for graphite. It is interesting that the yield of pinacol at graphite is similar to that at lead but the yield of the major unknown is greater at graphite. This suggests that the other byproducts must be significantly reduced when a graphite cathode is used.

3.4. *Alternative electrolytes*

The use of some alternative electrolytes led to significant improvements in yield. The improvement in yield in the case of tetraethylammonium bromide appears to be at the expense of minor byproducts since the quantities of major unknown and pinacol are about the same as for the standard conditions. In the case of tetraethylammonium chloride (used as the hydrate) the improved yield relative to the standard is nearly all at the expense of the major unknown. It is suspected that the presence of water reduces the yield of major unknown. Note the experiment in which tetraethylammonium bromide was used as the electrolyte and 1.8 mL of water (equimolar with AMN) was added to the mixture. In that case, although yields of desired product were very poor, none of the usual major unknown was formed.

Table 1. Electrocarboxylations of 2-acetyl-6-methoxynaphthalene[*]

Variable	*Cell/V*	*AMN/g*	*HN/g*	*Unk./g*	*Pinacol/g*	*Conversion*	*Selectivity*
Standard	6–12	2.74	16.29	3.75	0.55	87.7%	75.4%
Zinc	7–35	4.36	11.35	1.69	0.6	78.2%	64.3%
Stainless steel	8–11	2.74	13.75	3.93	0.46	86.3%	64.7%
Graphite	7–11	2.68	17.34	4	0.55	86.6%	81.3%
Mild steel	5–12	3.02	13.2	3.83	0.44	84.9%	63.1%
Aluminium	7–22	5.49	10.55	1.15	1.11	72.6%	59.1%
250 A m^{-2}	4–5	1.04	12.64	1.87	0.87	93.1%	73.5%
Et_4NBr	6–9	3.75	17.52	3.25	0.7	81.3%	87.7%
NaBr	7–21	9.93	8.93	0.79	0.61	50.4%	72.0%
$Et_4NCl;\cdot H_2O$	5–12	2.83	17.91	1.47	0.79	85.9%	84.7%
Et_4NBr; 1% H_2O	5–9	1.3	7.06	n.d.	1.7	93.5%	30.7%
690 kPa	6–11	2.75	17.44	3.86	0.19	86.3%	82.0%
5 °C.	8–14	3.7	15.8	2.84	0.26	81.5%	78.0%
5% Payload	6–7	2.07	8.18	1.24	0.11	79.3%	83.0%
20% Payload	7–23	5.7	24.1	6.08	5.17	85.8%	57.0%
NMP	25–30	2.86	13.27	3.43	1.44	85.7%	63.0%
CH_3CN[†]	4–15	2.56	19.51	1.51	2.23	87.2%	91.0%
1 L[‡]	6–10	7.5	110	n.d.	1.9	92.5%	96.0%

[*] All weights based on HPLC analysis of final electrolysis solution.

[†] Values erroneously high due to solvent evaporation during sample weighing.

[‡] Average of two runs; 690 kPa, $Et_4NCl;H_2O$; 1 L batch.

Tetraethylammonium salts were initially tried as lower-cost alternatives to tetrabutylammonium bromide; improved yields were unexpected. Another low cost electrolyte tried was sodium bromide. In that case, an insoluble material formed on the cathode, ultimately causing early termination of the electrolysis. It is suspected that sodium salts formed at the cathode precipitated to form an insulating layer.

It was not certain that chloride salts would work in this system, so it was a pleasant surprise to find no difference in operation of chloride or bromide salts since chloride salts are generally less costly. It may be that other anions would also work in this system but it is not likely any would be less expensive than chloride. The anode surface appears to corrode the same regardless of whether chloride or bromide salts are used. The lowest cost quaternary ammonium chlorides available from SACHEM (Austin TX) are triethylmethylammonium chloride and tetramethylammonium chloride. It is expected that the former will behave the same as tetraethylammonium chloride and that the latter would also work unless some insoluble salts formed.

3.5. *Effect of carbon dioxide concentration*

The effect of carbon dioxide concentration was evaluated by carrying out a run at 690 kPa. The carbon dioxide concentration at 690 kPa and 20 °C in DMF is expected to be 1.5 molar vs 0.3 molar at 138 kPa and 20 °C. The experiment at 690 kPa carbon dioxide gave a significantly better yield of HN than the standard conditions mainly at the expense of pinacol and the smaller unknown products. The yield of major unknown was unaffected. This is consistent with the expectation that a higher concentration of carbon dioxide will increase the odds of an AMN radical anion reacting with carbon dioxide before reacting by an alternative path to give byproducts.

3.6. *Effect of temperature*

Lowering the temperature also affects the carbon dioxide concentration. At 138 kPa carbon dioxide the solubility at 5 °C increases to about 0.5 molar. The experiment at 5 °C gave, as expected, a lower yield of pinacol but the HN yield suffered from lower conversion. The main problem with lower temperature is that the cell voltage increases because of higher solution resistance. This causes more heat to be generated, adding to the cooling load. It appears that increased pressure is a more attractive means of increasing carbon dioxide concentration.

3.7. *Effect of payload*

Lowering the concentration (payload) of AMN to 5% resulted in relatively less pinacol and major unknown but the yield suffered from the lower conversion. It is difficult to convert the last 1 wt % of AMN in this system. The reduced yield of pinacol for this experiment is expected because the AMN radical ions have a smaller chance of finding an unreduced AMN molecule with which to react.

Increasing the AMN concentration to 20% led to an inoperable situation. The solution became so viscous that it could no longer be pumped. Note that in that abbreviated run, the pinacol level was very high.

3.8. *Other solvents*

Two solvents other than DMF were tried in this reaction. *N*-methylpyrrolidinone (NMP) has solvent properties similar to DMF but was found not to be useful because solids formed on the electrodes, causing abnormally high cell voltages and ultimately premature termination of the reaction.

Acetonitrile is a commonly used electrochemical solvent and at first seemed to be a good alternative for this reaction because the product salts precipitated from solution during the electrolysis but did not initially plug the cell. The yield numbers given for the acetonitrile run in Table 1 are somewhat high because of sampling difficulties. The salts which precipitated from the acetonitrile solution during the run were moderately slow to filter, mainly due to the black sludge (thought to be colloidal aluminium) also formed.

The combination of higher pressure and tetraethylammonium chloride hydrate electrolyte was carried out in the 1 L system and resulted in the best yield obtained in this study.

3.9. *Conversion against time*

Graphs of concentration of reaction mixture components against time for the standard conditions and the 1 L experiments are shown in Figs 2 and 3. The graphs indicate the appearance of products and disappearance of AMN over the course of a run. Also included in the graphs are plots of the cell voltage over the course of the runs. It is evident from the graphs that the electrochemical carboxylation is quite

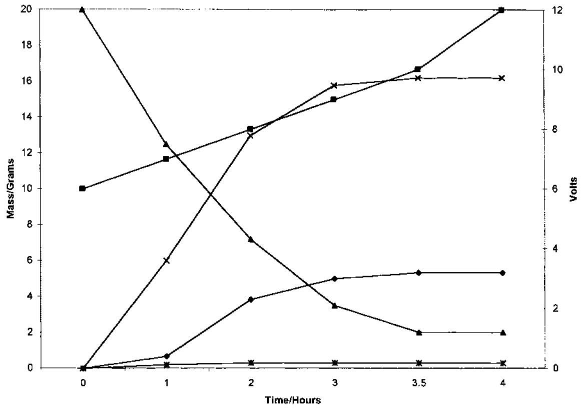


Fig. 2. Solution analysis of components of standard electrolysis. Key: (▲) AMN, (×) HN, (∗) Pinacol, (◆) unknown and (■) cell voltage.

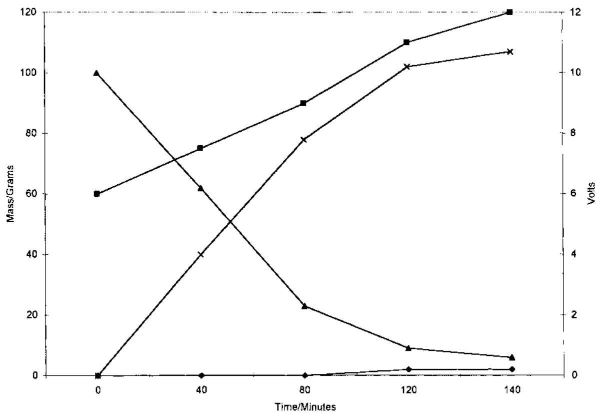


Fig. 3. Solution analysis of components of the 1 L electrolysis. Key: (▲) AMN, (×) HN, (◆) Pinacol and (■) voltage.

efficient for the first half of the reaction but not for the second half. As one would expect, pinacol is generally formed only in the early part of a run while the concentration of AMN is high.

3.10. *Major unknown byproduct*

Note in Table 1 a column of data is labelled 'Unk' for unknown. Most of the electrolyses produced an unknown product which eluted shortly after HN on HPLC analyses. This material has a u.v. spectrum similar to AMN so the AMN response factor was used to calculate a weight for this material but the weight given in the table might be grossly incorrect. However, the relative values of the unknown from run to run give a guide to means of reducing the production of this material. HPLC-mass spectral analysis indicated the mass of the unknown is 262. A logical structural assignment still eludes us.

3.11. *Reaction mechanisms*

A characteristic of the above reactions is that it is not possible to consume all the AMN even after prolonged electrolysis. Possible explanations are that the AMN is tied up in a nonreducible complex or a product is formed which is reduced at a less negative potential than AMN thus preventing the cathode voltage from attaining that necessary to reduce AMN. The latter is the favoured explanation. It is suspected that an aluminium salt formed from the anode corrosion products is reduced to aluminium metal at a potential less negative than the AMN reduction potential. In fact, there is evidence for that in voltammetric experiments described later.

3.12. *Scaleup to 1 L*

The average results of two 1 L scale runs are shown as the final entry in Table 1. The experiments went extremely well giving 94% and 98% selectivities based on solution analysis. This yield exceeds that of the 'standard' conditions by 20%. The improved yield of HN came at the expense of the major unknown (which is all but missing), pinacol and other minor byproducts. This result was the hoped for improved yield using a synergistic combination of conditions based on results from the earlier small-scale electrolyses.

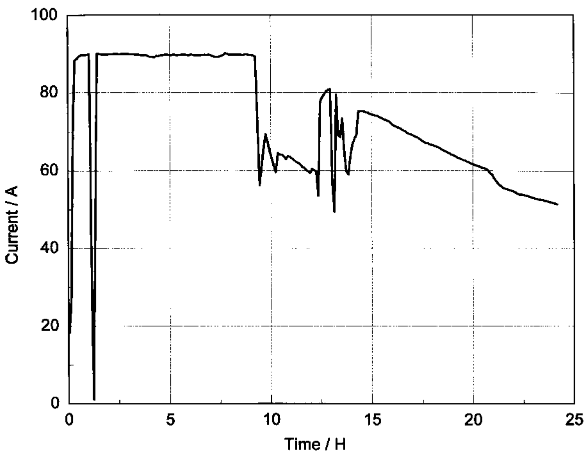


Fig. 4. Current against time for the 75 L pilot electrolysis.

3.13. *Scaleup to 75 L*

A description of the operation of a one-time batch pilot production aimed at providing several kg of HN for development of down-stream processes is in the experimental part. There were numerous operational problems associated with this adapted test unit that resulted in a low yield (58%) and current efficiency (30%). Figure 4 is a plot of current against time for the pilot operation. The first down-spike was for a short shutdown to repair a leaking gasket. The large current fluctuations starting at about 9 h and lasting until about 14 h were caused by overheating of the rectifier due to a cooling-fan failure. The electrolysis was ended at 24 h when new leaks developed and the electrolysis was more than complete. The 'West' cell voltage is shown in Fig. 5 and the 'East' cell exhibited a similar profile. Note that the cell-voltage variation was about the same as for

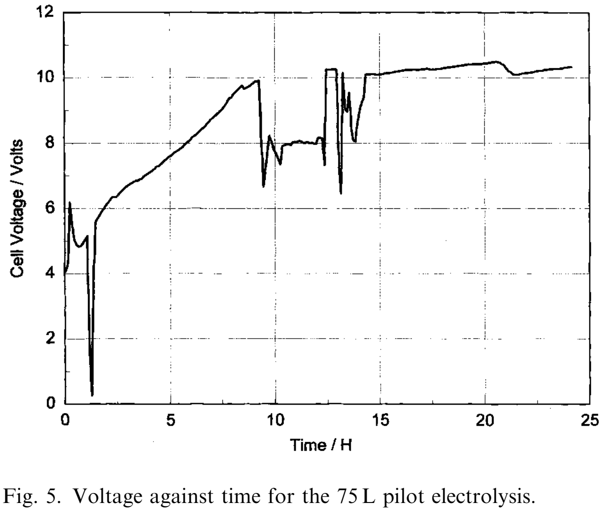


Fig. 5. Voltage against time for the 75 L pilot electrolysis.

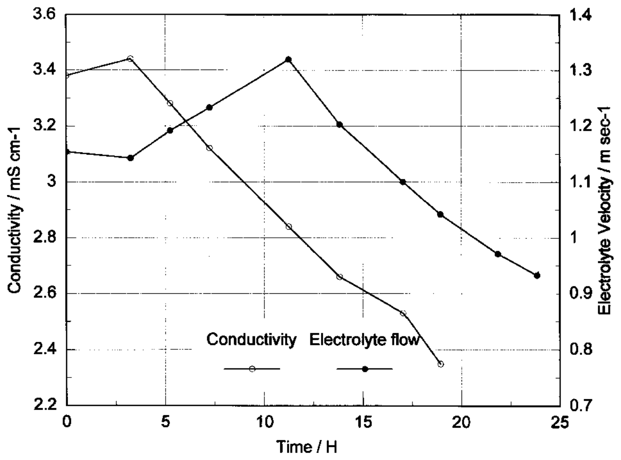


Fig. 6. Solution conductivity and flow velocity against time for the 75 L pilot electrolysis.

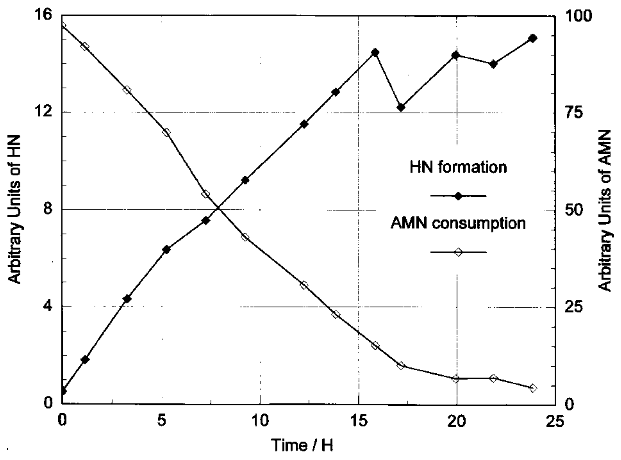


Fig. 7. Solution analysis of components of the 75 L pilot electrolysis.

smaller-scale electrolyses. Figure 6 shows the electrolyte flow and velocity in the cells. The velocity was estimated (and controlled) taking into account the change in cross-sectional area due to loss of aluminium from the anode. The aluminium loss was of the expected magnitude (slightly over stoichiometric), and the pattern of loss down the length of the cell was quite uniform with some irregularity at the entrance region. Electrolyte conductivity change is also shown in Fig. 6 and shows the expected decline. Figure 7 shows the concentration profiles for AMN and HN in arbitrary units during the electrolysis. These are similar to those in the small-scale electrolyses. Had a second test been conducted, with improvements in procedure and equipment, it is expected that results comparable to the 1 L operation could have been attained.

3.14. *Voltammetry*

Cyclic voltammetry of solutions of AMN in DMF containing tetrabutylammonium tetrafluoroborate were carried out at a glassy carbon working electrode. The voltammogram for AMN is shown in Fig. 8. The reduction peak occurs at -1.93 V vs Ag/AgCl and the reduction is reversible indicating that the radical anion reduction product of AMN is relatively stable and does not rapidly react with components of the solution. Addition of carbon dioxide to the solution causes nearly a doubling of the cathodic current, an anodic shift in peak potential and elimination of the reverse anodic current (Fig. 8). This indicates a very fast reaction of AMN radical anion with carbon dioxide followed by addition of a second electron.

Voltammetry of samples retained from finished electrolyses show a species present which reduces at a less negative potential than AMN (Fig. 9). This explains the fact that it is difficult to reduce all the AMN in a preparative run. It seemed reasonable that the material present at the end of a run, which reduces at less negative potential than AMN, would be an aluminium salt. Aluminium chloride was added to DMF and voltammetric analysis of the resulting solution produced a reduction peak at a potential similar to that obtained at the end of an electrolysis.

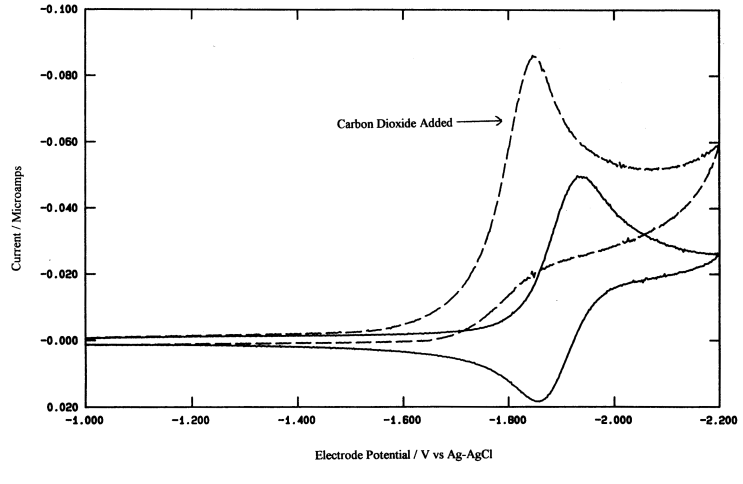


Fig. 8. Cyclic voltammetry of AMN in DMF containing 0.1 M Bu_4NBF_4 with and without added CO_2.

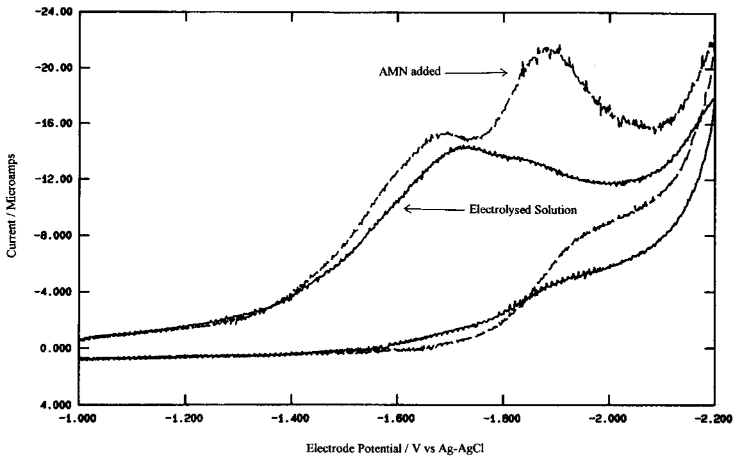


Fig. 9. Cyclic voltammetry of electrolysed solution with and without added AMN.

Acknowledgements

The authors would like to thank Dr Mark Jason, Dr Sa Ho and Kenneth F. Koncki (Monsanto Co.) and Dr J. David Genders (Electrosynthesis Co., Inc.) for aid and helpful discussion.

References

[1] Y. Ikeda and E. Manda, *Chem. Lett.* **1984**, 453.

[2] J. H. Wagenknecht, *US Pat. 4 582 577* (15 Apr. 1986).

[3] *Idem, US Pat. 4 601 797* (22 July 1986).

[4] G. Silvestri, S. Gambino and G. Filardo, *US Pat. 4 708 780* (24 Nov. 1987).

[5] A. S. C. Chan, T. T. Huang, J. H. Wagenknecht and R. E. Miller, *J. Org. Chem.* **60** (1995) 742 and references therein.

[6] A. S. C. Chan, J. Powers, C. J. H. King and C. Kim, unpublished work.

[7] S. Wawzonek and R. Gunderson, *J. Electrochem. Soc.* **107** (1960) 537.

[8] F. Hori, Y. Takiguchi and N. Urabe, *Denki Kagaku* **40** (1972) 455.

[9] R. Engels, C. J. Smit and W. J. M. van Tilborg, *Angew. Chem. Intl. Ed. Engl.* **22** (1983) 492.

[10] G. Silvestri, S. Gambino and G. Filardo, *Acta Chem. Scand.* **45** (1991) 987.

[11] G. Silvestri, F. Maspero, S. Gambino and G. Filardo, 'Mod. Methodol. Org. Synth'., Proc. Int. Symp. Org. React. (edited by T. Shono), Kodansha, Tokyo (1992), p. 443.

[12] A. P. Tomilov, *Russ. J. Electrochem.* **32** (1996) 25; *Elektrokhimiya* **30** (1994) 725.

[13] M. Tokuda, *Kagaku Kogyo* **45** (1994) 131.

[14] J. Chaussard, Electrochemical Synthesis of Fenoprofen, *in* 'Electrosynthesis from Laboratory, to Pilot, to Production' (edited by J. D. Genders and D. Pletcher), Chapter 8, p. 165, The Electrosynthesis Co., Inc., E. Amherst, NY (1990); I. Chaussard, M. Troupel, Y. Robin, G. Jacob and J. P. Juhasz, *J. Appl. Electrochem.* **19** (1989) 345.

[15] J. Y. Nedelec, 9th Int. Forum Electrosynthesis Chem. Ind. Electrosynthesis Co., Inc., Lancaster NY (1995).

[16] S. Derien, J. C. Clinet, E. Dunoch and J. Perichon, *J. Org. Chem.* **58** (1993) 2578.

[17] M. Troupel, J. Y. Nedelec and J. Perichon, 'Electroorg. Synth. [Manuel M. Baizer Meml. Symp.]' (edited by R. D. Little and N. L. Weinberg), Dekker, New York (1991) p. 355.

[18] A. Savall, *J. Phys. IV Colloq.* **4** (1994) 163.

[19] T. Inokuchi, H. Kawafuchi, K. Aoki, A. Yoshida and S. Torii, *Bull. Chem. Soc. Japan* **67** (1994) 595.

[20] G. D. Zheng, Y. Yan, S. Gao, S. L. Tong, D. Gao and K. Zhan, *Electrochim. Acta*, **41** (1996) 177.

[21] P. J. Harrington and E. Lodewijk, *Org. Proc. Res. & Dev.* **1** (1997) 72.