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Ceftibuten:[†] Development of a Commercial Process Based on Cephalosporin C. Part IV. Pilot-Plant Scale Electrochemical Reduction of 3-Acetoxymethyl-7(*R*)-glutaroylaminoceph-3-em-4-carboxylic Acid 1(*S*)-Oxide

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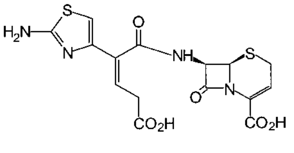
Abstract:

This contribution describes the operation of a pilot plant for the production of 3-exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylic acid 1(*S*)-oxide (4a) by the electrochemical reduction of 3-acetoxymethyl-7(*R*)-glutaroylaminoceph-3-em-4-carboxylic acid 1(*S*)-oxide (3a). This conversion is a key step in a new process for the production of Ceftibuten (1). The scale-up of the electrochemical reduction was demonstrated using a commercial flow-cell. The use of a novel type of extended-area tin cathode, which had been shown on a laboratory scale to produce significant improvements in the process, was successfully implemented in an ICI FM21-SP commercial-scale electrochemical reactor.

Introduction

The conventional route for the synthesis of Ceftibuten (**1**) uses a penicillin as the starting material.[1] The realization of a simpler route, starting with cephalosporin C (**2**), has been hindered by the high cost of cephalosporin C, and by the lack of a suitable route for the conversion of the 3-CH_2OAc group of cephalosporin C or 7(*R*)-aminocephalosporanic acid (7-ACA) to a 3-H cephem (see Part II).[2]



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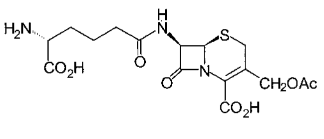

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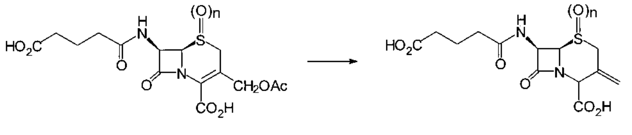
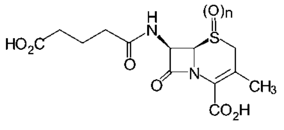
The achievement of a less costly, all aqueous commercial process for converting **2** to 7-ACA,[3] introduced new opportunities for accessing intermediates suitable for Ceftibuten manufacture, including one that has, as a key step, the electrochemical reduction of 3-acetoxymethyl-7(*R*)-glutaroylaminoceph-3-em-4-carboxylic acid 1(*S*)-oxide (**3a**) to 3-exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylic acid 1(*S*)-oxide (**4a**). The predominant electrochemical reduction product (**4a**) is the 1(*S*),4(*R*),7(*R*) enantiomer (see Part III).[4] The electrochemical reduction step was the subject of an extensive research effort at Colorado State University (CSU) and at the Electrosynthesis Company (ESC), in which different aspects of the process were studied and optimized.



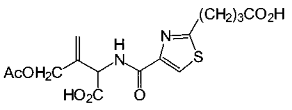
3a n=1
b n=0

4a n=1
b n=0

In the early stages of the project[2] electrochemical reduction work was centered on the reduction of the sulfide, **3b**. However, the electrochemical reduction intermediates derived from **3b** gave low yields of desired **4b** due to the competing formation of unwanted products, principally **5b** and **6**. This work led on to the identification of the sulfoxide, **3a**, as the best substrate(see Parts II III).[2,4]



5a n=1
b n=0



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Typically, electrochemical process development includes optimization of electrode materials, current density, temperature, composition of the electrolyte, and other parameters relevant to the performance of the system. This is initially achieved by the application of electroanalytical techniques such as cyclic voltammetry, followed by small-scale preparative electrolysis in glass cells and laboratory flow cells; solution volumes of up to 1−2 L are usually processed. The objectives of the pilot-plant work described in this report were (i) to validate the tin cathode and determine the best

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[†] Ceftibuten was discovered by Shionogi and Co. Ltd., Osaka, Japan, and licensed to Schering Plough Corporation, Kenilworth, New Jersey. The drug is manufactured by Shionogi.

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(1) Yoshioka, M. *Pure Appl. Chem.* **1987**, *59*, 1041.

(2) Part II: Bernasconi, E.; Genders, D.; Lee, J.; Longoni, D.; Martin, C. R.; Menon, V.; Roletto, J.; Sogli, L.; Walker, D.; Zappi, G.; Zelenay, P.; Zhang, H. *Org. Process Res. Dev.* **2002**, *6*, 152.

(3) Cambiaghi, S.; Tomaselli, S.; Verga, R. (Antibioticos, S.p.A). U.S. Patent 5,424,196, 1995.

(4) Part III: Bernasconi, E.; Lee, J.; Sogli, L.; Walker, D. *Org. Process Res. Dev.* **2002**, *6*, 169.

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form for large-scale work, (ii) to demonstrate the feasibility of the electrochemical reduction process on a larger scale, and (iii) to produce sufficient quantities of **4a** to be used in downstream-processing studies.

In the small-scale studies conducted at CSU and ESC it was shown that the following set of experimental conditions produced nearly quantitative yields of **4a** with undetectable levels of **5a** and **6**:

temperature	10−15 °C
composition of the medium	0.2 M potassium hydrogen phosphate buffer
current density	100−200 mA cm^{-2}
cathode material	Sn mesh

Results using tin plate and tin wire, in place of the tin mesh, were inferior (see Table 10 in Part II).[2] The selection of the cathode material was of critical importance to the success of the process. The rate of the hydrogen-evolution reaction, the principal competing cathodic process, is highly dependent on the electrode material; therefore, it is possible to minimize the hydrogen-evolution reaction by choosing the appropriate cathode.[5] Hg, Pb, Cd, Ni, Cu, Sn, Ag, steels, Hastelloy, and different types of carbon are some of the possible materials available.

Excellent results were obtained using a mercury cathode; however, its use in a large-scale process would present numerous disadvantages, not only for environmental reasons but also because it would exclude the use of modern commercial electrochemical flow reactors of the plate and frame type. The results obtained using a tin cathode were also very encouraging. We projected that by using an extended-area tin electrode we would increase the current efficiency, reduce plant requirements, and thereby reduce the capital cost. An expanded mesh tin material, shown by the photograph in Figure 1, was designed and built; its dimensions are long aperture, 4.75 mm; short aperture, 2.38 mm; width of strand, 0.56 mm; thickness, 0.50 mm; and weight, 0.64 kg/m^2.

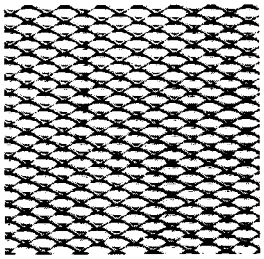

Figure 1. **Photograph of the expanded Sn mesh.**

The limiting current density in a process controlled by mass-transport to the electrode is proportional to the electrode area,[6] as described by the equation:

$$i_L = k_L A n F c^{\infty}$$

where i_L is the limiting current, k_L is the mass-transport coefficient, A is the electrode area, n is the number of electrons transferred in the process, F is Faraday's constant, and c^{∞} is the bulk concentration of the substrate. To estimate the effective area of the tin mesh electrode, current−potential curves were recorded using, as a model, the reversible one-electron reduction of ferricyanide to ferrocyanide:

$$\mathrm{Fe(CN)_6}^{3-} + e^- \rightarrow \mathrm{Fe(CN)_6}^{4-}$$

The results of measurements on planar Sn and on stacked Sn expanded mesh are shown in Figure 2. The limiting current increased by a factor of approximately 4.4 when the planar Sn electrode was replaced with six layers of Sn mesh. In light of these results it is possible to assume that a reaction on a planar tin cathode would produce results similar to those from a reaction on a tin mesh cathode conducted at a current density 4.4 times higher. The reaction time using the tin mesh cathode would therefore be 4.4 times shorter for a similar cell size.

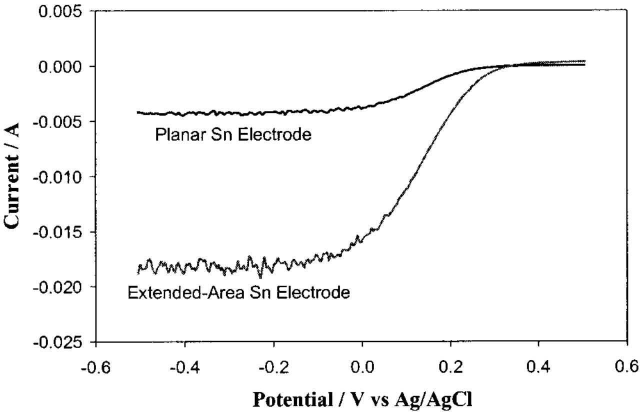

Figure 2. **Current−potential measurements with Sn mesh electrode.**

In flow-cell experiments, the use of Sn mesh as a cathode material caused an increase in the yield of more than 10%, and the overall current efficiency was increased by about 50%. This was in agreement with the observations from previous cyclic voltammetry studies; the use of an efficient extended-area electrode allows the electrode potential to remain lower, thereby reducing the extent of the hydrogen-evolution reaction.

The pilot-plant work represented a scale-up factor of approximately 200 in terms of electrolyte volume from the previous work done in laboratory ElectroCell AB Multi-Purpose cells; the overall results were similar to those obtained on the smaller scale: material yields of >95% at 99% conversion were achieved, and the current efficiency was still 4−6%. An extended-area tin cathode similar to that used in the research effort on the laboratory scale was successfully adapted to the ICI FM-21 cell used in the pilot plant. A diagram of the entire plant can be seen in Figure 3.

Results and Discussion

A total of 13 reactions were conducted; 2.84 kg of **3a** were used in each reaction, with the exception of the last run, where 2.34 kg of **3a** were employed. The total starting material consumed, therefore, was 36.42 kg. With the

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(5) *Electrosynthesis from Laboratory, to Pilot, to Production*; Genders, J. D., Pletcher, D., Eds.; The Electrosynthesis Co., Inc.: 1990.

(6) Southampton Electrochemistry Group. *Instrumental Methods in Electrochemistry*; Kemp, T. J., Ed.; Ellis Horwood Series in Physical Chemistry; Ellis Horwood Limited Publishers: Chichester, 1985.

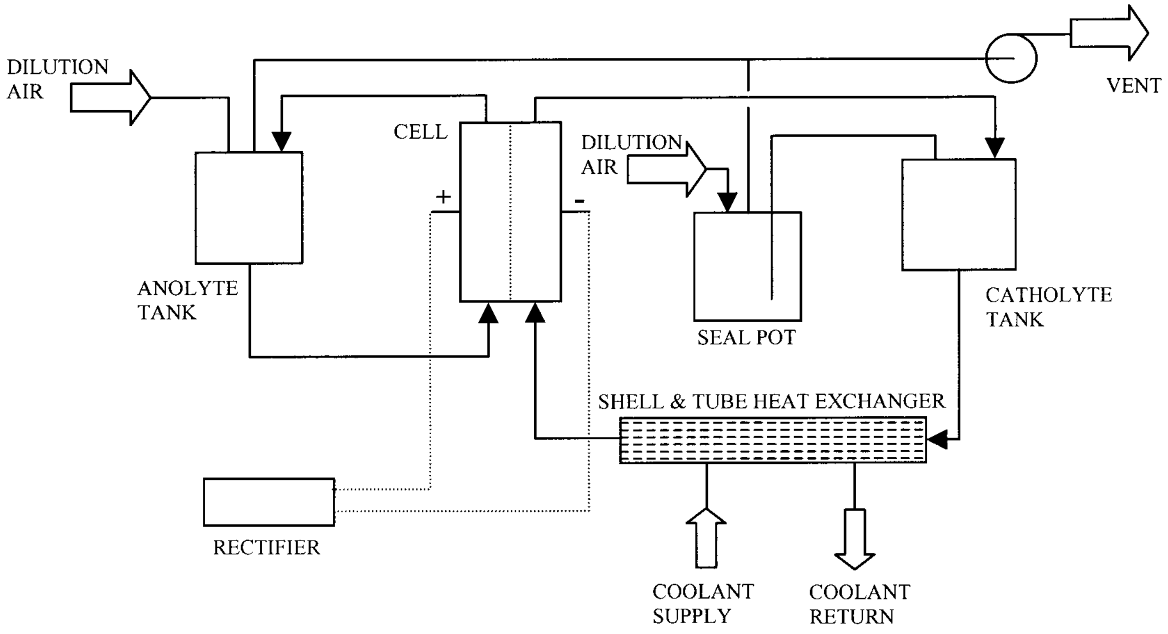

Figure 3. **Diagram of the pilot plant.**

Table 1. **Summary of the results and conditions in the pilot-plant experiments**

reaction no.	current density/kA m^{-2}	pH	cell voltage/V	reaction time/h	temperature/°C	conversion[a] %	yield[b] %
372-3	1.20	7.1−7.4	5.8−6.2	17.0	12−13	88	74
372-6	1.20	7.1−7.4	6.4−6.6	12.0	10−12	97	82
372-7	1.60	7.1−7.3	7.1−7.3	10.0	13−14	93	78
372-8	1.60	7.1−7.3	7.2−7.3	10.0	11−13	94	85
372-9	2.00	7.1−7.3	7.6−7.8	7.0	17−18	91	82
372-10[c]	2.00	8.0−8.2	7.6−7.7	7.25	18−19	99	84
372-11	1.60	7.9−8.1	7.1−7.3	11.0	13−14	99	96
372-12	1.60	7.9−8.1	7.0−7.2	12.0	12−13	99	95
372-13	1.60	7.9−8.1	7.0−7.2	12.0	13−14	99	94
372-14	1.60	7.9−8.1	7.0−7.2	12.0	13−14	99	97
372-15	1.60	7.9−8.1	7.0−7.2	12.0	13−14	99	93
372-16	1.60	7.9−8.1	7.0−7.2	12.0	13−14	99	90
372-17	1.60	7.9−8.1	7.0−7.2	10.0	13−14	99	89

[a] Conversion: (mol of starting material disappeared/initial mol of starting material) × 100. [b] Yield: (mol of product/initial mol of starting material) × 100. A starting material purity of 90 wt % was assumed. The peak area corresponding to the second isomer of the sulfoxide (R-isomer), usually accounting for 4−6% of the total, was not included in the calculations. [c] Due to control problems, the pH reached a value of approximately 10 for ~30 min.

exception of the first reaction, where only one anode was used, the cell configuration was as described above, that is, an anode at either side of the tin mesh cathode.

The results obtained are summarized in Table 1. It is evident that the yield was optimized at a current density of 1.6 kA m^{-2}, and a pH of approximately 8.0. The conversions under these conditions were almost complete, and the material yields were close to quantitative. It is worth noting that the second isomer of the sulfoxide, usually accounting for approximately 5% of the main product peak, was not included in the calculations, and therefore the actual material yields are higher than those reported here. As expected, there is a significant decrease in the reaction rate as the starting material is depleted; a relatively large amount of charge is therefore necessary to achieve conversion of the last 5−10% of **3**.

At the end of the project the cell was disassembled, and its components were visually examined. The following observations were made:

(i) The membrane did not show any obvious signs of deterioration; some discoloration was observed, but a voltage increase that would have indicated damage to the membrane was not observed during the reactions. The same piece of membrane was used for all the reactions. On the basis of the above information, short-term damage to the membrane is unlikely in this process.

(ii) There was no obvious difference in the appearance of the anodes after the reactions. The process conditions, that is, relatively low current density, low temperature and acid concentration, are mild for the type of electrode material used, that is, oxygen-evolving DSA (dimensionally stable anode), low pH. An electrode-coating lifetime of 1−3 years can probably be expected, and at the end of this period recoating can be applied to the same substrate.

(iii) Likewise, the surface of the cathode did not show any obvious signs of degradation. The concentration of tin in the product mixture was determined by atomic absorption; the results are presented in Table 2.

Table 2. **Concentration of tin dissolved in the reaction mixtures**

reaction no	Sn/ppm	reaction no	Sn/ppm
372-3	17	372-12	22
372-6	15	372-13	32
372-7	35	372-14	22
372-8	40	372-15	23
372-9	30	372-16	22
372-10	39	372-17	25
372-11	23		

(iv) Assuming an average loss of 1.5 g of tin in every reaction, the effect this rate would have on a solid tin electrode would be limited. A total loss of approximately 0.5 kg of tin (based on 1 reaction/day during a period of 365 days) would probably not affect the performance of the cathode, whose dimensions are approximately 24 × 93 cm. The mechanical properties of the tin cathode, however, should be the subject of further consideration. It was found that because of the malleability of the cathode structure assembling and disassembling the cell required special care. The current cathode configuration consists of six layers of tin mesh welded onto a solid sheet of tin; a more rigid structure with tin mesh covering a different metal substrate is currently being considered as an alternative.

(v) Current densities of up to 2 kA m^{-2} were used; although these current densities are probably not deleterious to the reaction, it was not possible to dissipate the extra energy generated in the process, and the temperature rose by 4−5 °C, with a consequent small decrease in the material yield. A chiller with a larger capacity would therefore be necessary to operate the process at higher current densities.

Process Economics

The overall criterion used to determine the economic viability of the process, as in other chemical processes, is the return on investment. In the specific case of an electrochemical plant the following figures of merit are taken into account when attempting to optimize the economics: current efficiency, selectivity, electrical energy consumption, cell voltage, energy efficiency, current density, and lifetime of the electrodes. The capital cost is typically estimated by taking the required cell cost as a basis for calculations and applying a multiplier that depends on the size and complexity of the plant. On the basis of experimental evidence, a total electrode area of 12.6 m^2 is required to achieve a rate of production of 40 T/year. The estimated cell cost associated with this electrode area is $365,000; if a typical multiplier of 4−5 is applied, the total cost of the plant is $1,400,000−1,800,000.

Conclusions

A high-surface-area tin cathode was built, fitted into a small commercial-scale electrochemical reactor and the equipment used to study the electrochemical reduction of 3-acetoxymethyl-7(*R*)-glutaroylaminoceph-3-em-4-carboxylic acid 1(*S*)-oxide (**3a**) to 3-exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylic acid 1(*S*)-oxide (**4a**). The pilot plant reactions gave essentially the same, nearly quantitative yields as those that were obtained in laboratory electrochemical cells.

The process was not taken to a commercial scale for Ceftibuten manufacture because the market did not develop.

Experimental Section

Equipment. All the reactions were carried out in an ICI Model FM21SP plate and frame flow cell equipped with two electrode pairs. The anode was separated from the cathode by a Nafion 350 cation-exchange membrane. The cathode consisted of a flat tin substrate to which five layers of tin mesh were welded on either side. Two DSA (dimensionally stable) anodes (ICI ES2 on titanium flat plate oxygen-evolving electrodes) were used, with one placed on either side of the cathode. The Nafion 350 cation-exchange membrane, pretreated by soaking in deionized water for several days, was placed between each electrode pair. Each electrode had a surface area of 0.21 m^2 for a total of 0.42 m^2. The membrane-to-anode gap was 0.5 cm. A diagram of the cell is shown in Figure 4.

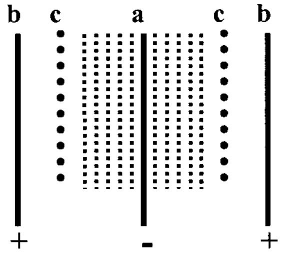

Figure 4. **Schematic diagram of the FM21-SP cell. (a) Cathode assembly, stacked-Sn mesh on a Sn substrate; (b) oxygen-evolving anode; (c) Nafion 350 cation-exchange membrane.**

The catholyte reservoir was a 113 L closed-head polyethylene tank. The anolyte reservoir was a 378 L fiberglass tank. Both tanks were calibrated with water before use. Solutions were circulated through the system using two March model TE5.5C MD magnetically coupled centrifugal pumps. The flow rates were measured using two EXAKT model MA200 polysulfone rotameters equipped with model MAF3M magnetic floats and model Z31 unlatched limit switches to ensure that a minimum flow was always maintained. The catholyte solution pH was monitored and controlled using a Horizon 5997 pH controller with a pH electrode and separate acid and base feed lines placed at the cell catholyte exit. The catholyte solution temperature was controlled by passing it through a Corning model 600GRB glass shell and tube heat exchanger before it entered the cell. The coolant for the heat exchanger consisted of a 33% (vol) solution of propylene glycol in water. It was cooled by passing through a FTS model RC500 recirculating cooler. The cell and reservoirs were contained within two PVC drip trays each containing an I^2R model SP-AB spill sensor to detect possible leakages. Power was supplied to the cell by a Rapid model SCRA 4000-18 power supply connected via a 1000 A/100 mV shunt to the current manifold. Current readings were taken directly off the shunt using a multimeter. The power supply was connected via a relay to the main plant control system.

Electrolyte Preparation. The anolyte solution for all batches consisted of approximately 60 L of 0.5 M sulfuric acid prepared by diluting concentrated acid (95−98%, ACS reagent, Aldrich Chemical Co.). The anolyte strength was tested at least once per batch and deionized water added as required to maintain the strength. The initial anolyte solution was reused for all batches produced. Each batch of catholyte solution was prepared by dissolving approximately 2.84 kg of 3-acetoxymethyl-7(*R*)-glutaroylaminoceph-3-em-4-carboxylic acid 1(*S*)-oxide in up to 56.7 L of 0.2 M potassium hydrogen phosphate (made from 98 + %, ACS reagent, Aldrich Chemical Co.). This produced a concentration of approximately 50 g/L of starting material. The pH of the solution was then adjusted using concentrated potassium hydroxide (45 wt %).

Reaction Procedure. In a typical reaction, 56.7 L of starting material were made up as described and loaded into the catholyte reservoir. After the solution circulated for a few minutes at a typical flow rate of 11−13 L min^{-1}, the anolyte was sampled for concentration and adjusted if necessary. The pH electrode was calibrated and inserted into the catholyte outlet line. The solutions were then circulated. The sealpot was checked for water level and topped off if required because it was necessary to maintain the slight positive pressure in the hydrogen gas line. The lab blower was then started and the air flow measured in both the anolyte and catholyte gas lines. The recirculating chiller was started to bring the temperature of the catholyte solution down to the required value. In addition, the nitrogen purge was initiated manually to remove all air from the system. Gas samples were taken from the hydrogen gas line and analyzed for oxygen content by gas chromatography. When the oxygen level had dropped to 0.5% vol/vol or less and when the temperature was at the desired value, the power supply was turned on and a constant current applied. During the run samples were typically taken every hour to evaluate progress. Voltage, temperature, and volume readings were also recorded. In addition, the pH was maintained at the required value by addition of 45% KOH or 85% H_3PO_4. When the required conversion was achieved (by HPLC analysis), the power was turned off and the system purged with nitrogen to remove all hydrogen. The pH of the catholyte was also adjusted down to 4.3, and then it was transferred to a storage drum. On those occasions where it was necessary to continue a batch run the following day, the catholyte pH was adjusted to around 7.0 after the power was shut down and nitrogen purge initiated, and the cell was left flooded overnight. The current leads to the cell were also disconnected to avoid current reversal (battery effect) in the cell.

Analytical Section

Analysis of Catholyte Solution. Catholyte samples were taken at 1-h intervals during the run and analyzed for starting material and product using the following HPLC method: column: YMC J'sphere M80-C18; particle: S-4 μ 80A; size: 4.6 × 250 mm; mobile phase:94% 0.025 M KH_2PO_4; pH = 4.2; 6% CH_3CN; flow rate: 1.2 mL/min; detector: UV @ 215 nm. A typical chromatogram can be seen in Figure 5.

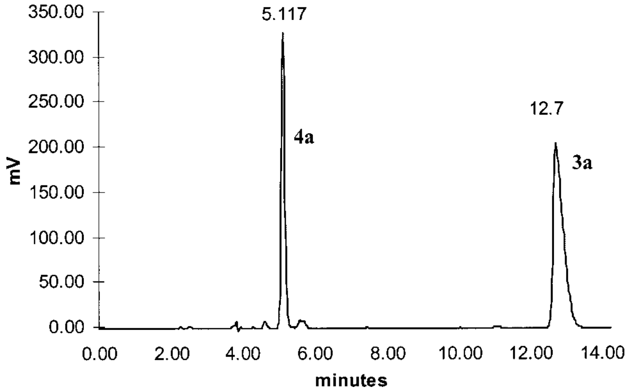

Figure 5. **Chromatogram of a sample of catholyte.**

Analysis of Catholyte Gases. Samples of the gas in the catholyte circuit were analyzed periodically by gas chromatography to ensure that the oxygen levels in the hydrogen that were being evolved at the cathode were below the flammable limit. A molecular sieve column and thermal conductivity detector were employed, and the carrier gas was helium.

Safety Considerations. Particular attention was paid to the safety issues related to the potential presence of hazardous hydrogen−oxygen mixtures. These mixtures are flammable at hydrogen concentrations between approximately 4 and 96 vol %. In the catholyte circuit flammable gas mixtures can be produced by penetration of small amounts of air from the atmosphere or oxygen produced at the anode. In the anolyte, leaks of hydrogen from the cathode side could also give rise to hazardous mixtures. To prevent these situations, the following measures were adopted:

(i) A small positive pressure was continuously maintained in the catholyte gases.

(ii) Both catholyte and anolyte gases were diluted with enough air to ensure that the hydrogen concentration was below 1%.

(iii) The presence of oxygen in the catholyte off-gases was periodically monitored by GC.

Gas Handling System. The anode reaction product (mainly O_2) was first diluted with a measured amount of air and then passed through a de-mister consisting of a 304 stainless steel woven fabric wound around stainless steel cooling coils and all contained in a 19 L polyethylene drum. From here it was drawn by a Nalge model 71320-0075 explosion-proof lab blower and exhausted to the outside atmosphere. The cathode gaseous reaction product (hydrogen) traveled under slight positive pressure (to prevent ingress of air) from the cell exit into the catholyte reservoir and then to a sealpot where it was then diluted to safe levels with a measured amount of air and exhausted to the atmosphere by the lab blower. The actual flow of dilution air for the anolyte as well as catholyte off gas was measured periodically using a Kurtz model 444 air velocity meter. In addition, the composition of the catholyte off-gas was analyzed periodically for oxygen content by gas chromatography.

Safety Interlock System. The plant was controlled by an I^{2}R model SP-1 alarm and cutoff. This monitored the process for unsafe conditions and was designed to initiate the safety interlock system in the event of an unsafe condition. The unsafe conditions are listed below.

anolyte flow rate	low
catholyte flow rate	low
cell spill sensor	activated
tank spill sensor	activated
lab blower inlet vacuum	low
hydrogen gas line pressure	low

In the event that any of these conditions occurred, the power supply to the cell was automatically shut off, and a nitrogen purge was automatically introduced via an activated solenoid valve into the catholyte reservoir. In addition, the shutdown sequence could be activated manually.

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