J. Serb. Chem. Soc. *65*(1)47-53(2000)
JSCS-2724

UDC 615.779:541.138.3:541.135.52
Original scientific paper

Electroreduction of cefetamet on mercury platinum and gold electrodes

M. AVRAMOV-IVIĆ,[1] V. KAPETANOVIĆ,[2] M. ALEKSIĆ2* and P. ZUMAN[3]

[1]*ICTM, Department of Electrochemistry, Njegoševa 12, YU-11000 Belgrade, Yugoslavia,*
[2]*Faculty of Pharmacy, Department of Physical and Analytical Chemistry, Vojvode Stepe 450, YU-11000 Belgrade, Yugoslavia and* [3]*Department of Chemistry, Clarkson University, Potsdam New York, USA*

(Received 19 May, revised 12 October 1999)

The electroreduction of cefetamet (CEF) using gold and platinum electrodes has been investigated in slightly alkaline medium (pH 8.40) where adsorption, previously observed at mercury electrode, was pronounced. This investigation was performed in order to determine whether the adsorption interfers with the reduction process even at solid electrodes and to compare with a mercury electrode.

Keywords: cefetamet electroreduction, platinum, gold and mercury electrode.

The b-lactam antibiotics, penicilins and cephalosporins, play a very important role in human pharmacology on account of their broad antibacterial activity spectrum.[1,2] Their activity is exerted through the inhibition of the biosynthesis of the bacterial wall, which leads to lysis of the microorganisms. However, cephalosporins have the additional advantage of being applicable to penicilin-allergic patients and begin active against penicilin-resistant microorganisms in some instances.

Cephalosporins are generally electroactive and give a faradaic response on an electrode (mercury or solid) immersed in their solution. Their electroactivity is due either to the presence of oxidisable or reducible substituents, or to the double bond in the dihydrothiazine ring common to all b-lactams.

All cephalosporins containing a substituent at position 3 of the cephem nucleus undergo reduction of the $C_3 = C_4$ double bond with the subsequent cleavage of the related substituent. This reduction seems to be totally irreversible.[3,4]

Certain cephalosporins contain additional, or possibly other reducible groups which are electroactive. Most of the new generation cephalosporins posses a reducible methoxyimino group in the side-chain at position 7. One of them is the third generation cephalosporin – cefetamet-Na investigated in this work. Its structure is presented in Fig. 1. A literature search related to the reduction mechanism of this methoxyimino group showed that the investigations were performed in acid

* Serbian Chemical Society Member

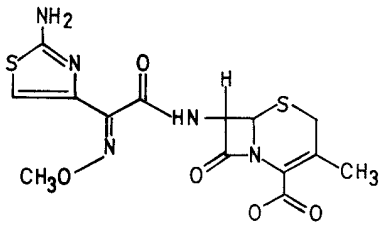

Fig. 1. Cefetamet-Na.

medium only. All authors believe that the electroactivity is due to the reduction of the azomethine (C=N) double bond in the methoxyimino group, but there are different opinions about the number of electrons involved. Some believe that there is a two electron transfer,[5,6] while others assume a double two electron reaction of the methoxyimino group *via* a hydroxylamine intermediate to give the corresponding amine and methanol, occurs.[7,8] The results of this study obtained using controlled potential electrolysis,[9] support the second hypothesis about a double-two-electron reduction.

The adsorption of cephalosporins on mercury electrode surface has been reported to play an influential role in the electrochemical behavior of many (or probably most) cephalosporins.[4,10–12] This adsorption seems to be the main event causing the complex electrode behavior. It affects the linearity of the peak current to concentration dependence and the polarographic wave splits into two waves which hinders the study of the reduction mechanism.

The adsorptive properties of cephalexin, cefaclor and 7-aminodesacetoxycephalosporanic acid were examined by applying sensitive AC polarography in order to find the optimal conditions for the distinct adsorption effect and to determine the ionic species participating in the adsorption.[13] It was found that cationic and zwitterionic forms of most of the investigated cephalosporins antibiotics showed intensive adsorption, while the anionic forms (present in alkaline media), exhibited strong repulsive forces between the adsorbed species, indicating these negative charged forms are adsorbed only to a minor extent.

Most papers reported on the reduction of cephalosporins and only a few were concerned with their oxidation at solid electrodes.[14–16] In an extensive electroanalytical study of several drugs at rotating gold and platinum disc electrodes, Bishop and Hussein[17] examined the cathodic and anodic activity of certain cephalosporins at both electrodes in acidic and alkaline medium. Only cefalexin was reported to show two anodic waves at the gold electrode in 0.1 mol dm^{-3} sulphuric acid and at high concentrations ($>10^{-3}$ mol dm^{-3}), but no activity was found at the platinum electrode. No attempts were made to elucidate the oxidation mechanisms.

The aim of this work was to continue the investigations on the reduction of cefetamet using mercury, gold and platinum electrodes in order to find out whether the adsorption, previously observed at mercury electrodes[9] interferes with the

reduction process even at solid electrodes. Since it was proved[13] that the adsorption is lower in alkaline media, and the reduction has not been studied enough in this pH regia, this paper deals with voltammetric investigations of cefetamet at pH 8.40.

EXPERIMENTAL

All the experiments were performed in a standard three electrode electrochemical cell. Gold (S = 4 cm^2) and platinum plates (S = 1 cm^2) were used as the working electrodes, with a 60 ml volume of electrolyte. A platinum wire served as the counter electrode and in all the experiments a saturated calomel electrrode was the reference electrode. Standard electrochemical equipment was used for the cyclic voltammetry measurements: a potentiostat Pine RDE 4 and a Philips PM 138 $X_tY_1Y_2$ recorder.

Polarographic measurements were performed with an EG&-G Princeton Applied Research Corp. (PAR) Model 164A polarographic analyzer, coupled with a PAR 303A static mercury drop electrode (SMDE) (drop size: medium; area of the drop, 0.017 cm^2). The cell (PAR model K 0060) was fitted with an Ag/AgCl saturated KCl polarographic reference electrode, and a platinum wire was connected to the 303 SMDE. The capillary of the mercury electrode had a bore diameter of 0.016 cm and a length of 12.7 cm.

The surface preparation of the solid electrodes has been described in previous papers.[18,19]

All investigations were carried out with Cefetamet-Na (standard) produced by Hoffmann La Roche (Basel, Switzerland). Stock solutions of the antibiotic were prepared daily, dissolving in water a suitable amount of Cefetamet-Na without purification. All other reagents and chemicals used in this study were of analytical grade. In all experiments 18 MW cm water was used. The experiments were performed at room temperature.

RESULTS AND DISCUSSION

On the mercury electrode in 0.1 M K_2SO_4 at pH 8.4, the investigated cephalosporin shows two well defined cv (cyclo-voltammetric) reduction peaks as presented in Fig. 2, the first one at –1.07 V and the second one at –1.22 V. No anodic peaks were observed at polarization rates of 5–1000 mV s^{-1} indicating a two step irreversible reduction process. Poisoning of the mercury surface is obvious as during the cycling all the values of the currents decrease as is shown in Fig. 2.

It was observed that in the second cycle both reduction peaks apear at slightly more negative potential than the same peaks in the first cycle. This can be explained by poisoning of the mercury electrode during the first cycle. The most probable

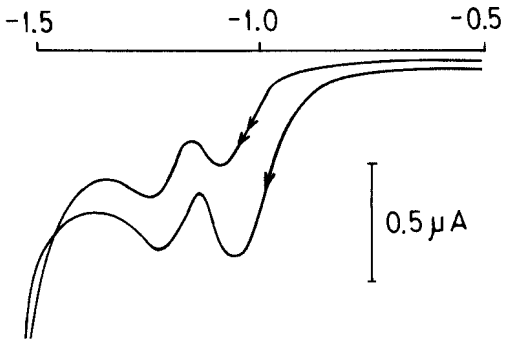

Fig. 2. Cyclic voltammogram of $3.5 \cdot 10^{-4}$ M CEF on a mercury electrode, in 0.1 M K_2SO_4 + NaOH (pH 8.4), sweep rate 50 mV/s.

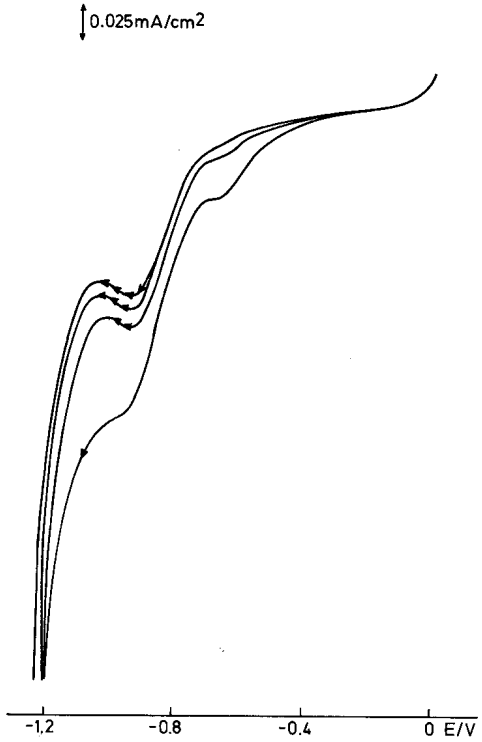

Fig. 3. Cyclic voltammograms of $3.5 \cdot 10^{-4}$ CEF on a Au electrode in 0.1 M K_2SO_4+NaOH (pH 8.4) from the first (>) to the fourth cycle) (>>>>), sweep rate 50 mV/s.

process is the adsorption of different species during the formation of the two reduction peaks in the first cycle which causes the more negative appearance and the lower peak currents in the second cycle.

The electrochemical activity of CEF on gold in 0.1 M K_2SO_4 (pH 8.4) has been investigated. The potential was cycled from 0.0 to –1.2V (*vs.*SCE) at a sweep rate of 50 mV s^{-1}. Under these experimental conditions, two reduciton waves (the first at – 0.65 V and second one at – 0.95 V) were observed in the presence of CEF (Fig. 3). The height of the current of both waves decreases with number of cycles in the whole range of the potential, which indicates a strong poisoning of the gold electrode surface as is presented in Fig. 3. For the gold electrode, the position of the both peaks potential is shifted to the slightly more positive values with the number of the cycles, starting from the first to the fourth. The peak currents decrease with the number of the cycles. This is specialy pronounced in the case of the first peak. After the third cycle, this peak no longer appeared. In the case of the second reduction peak of CEF, only a lowering of the peak currents is observed.

It was surprising that the reduction peaks are shifted to slightly more positive potential values with cycling and, in the same process, the peak currents apparently decrease especialy in the case of the first reduction peak. It can be supposed that the observed effects are the consequence of the changed electrode surface in the presence of CEF and its reduction products after the first cycle. From Fig. 3 it is

clear that during four cycles, the heights of the peak currents approach a constant value with each cycle. The time consumed for the occurrence of the four cycles (under the experimental conditions described in the Figure caption) is 96 s. That suggests that the adsorption process is the rate determining step and can be further examined in detail by AC polarography.

If a clean gold electrode is placed into electrolyte containing CEF during one minute before the electrochemical measurements, the inhibition of both CEF reduction waves is obvious in the first potential cycle. This confirms that physisorption occurs without any electrochemical process or electrochemical cycling and that the process of physisorption must be included in any speculation about the mechanism. Because of the very fast poisoning of the electrode curface, stationary measurements with a very slow sweep rate cannot be applied as one minute is enough for complete poisoning of the gold electrode surface. It the cycle begins at the value of the potential at which the first wave is observed and at the same moment the CEF is added to the electrolyte, the first wave is not observed and second wave is smaller than in the case when CEF is present in the electrolyte before cycling. This indicates the necessity of CEF adsorption before the appearance of the first wave during electrochemical reduction on a gold electrode. The fact that during four cycles the heights of the peak currents approach a constant value suggests that the products of CEF reduction during the formation of the first peak are not responsible for the main poisoning of the gold electrode and the prevention of the formation of the second peak.

In the potential range from 0.0 V to –1.00 V on a Pt electrode, two waves for CEF electroreduction can be observed, as is displayed in Fig. 4. Comparing with Fig. 3 (with an Au electrode) it is obvious that both waves of the CEF reduction

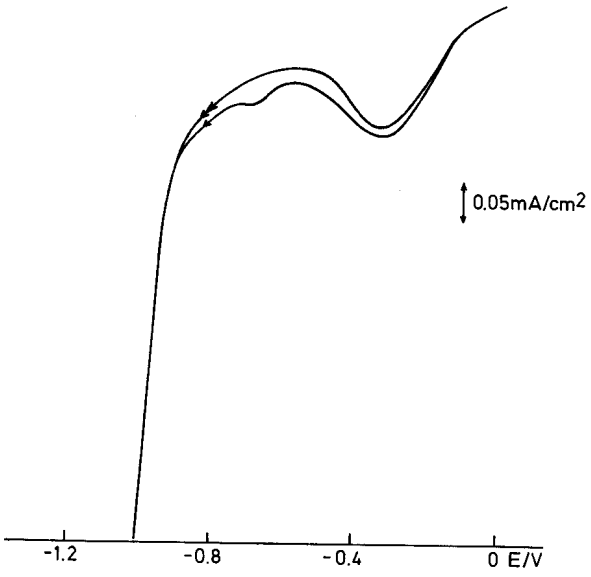

Fig. 4. Cyclic voltammogram of $3.5 \cdot 10^{-4}$M CEF on a Pt electrode in 0.1 M K_2SO_4+NaOH (pH 8.4) from the first (>) to the second cycle (>>), sweep rate 50 mV/s.

appear at more positive potential on the Pt electrode than on the gold electrode (the first one at – 0.325 V and second one at – 0.675 V). From Fig. 2 it is clear that on a mercury electrode both CEF reduction peaks appear at the most negative values of the potential.

Poisoning of the Pt electrode surface is also observed during CEF electrochemical reduction. The currents decrease with the number of cycles, as was observed on the gold electrode. In the second cycle, the position of the first peak is shifted to a slightly more negative potential and the currents of the second peak disappear.

Taking into account the values of the potentials of the appearance of the maximal currents of the first and second wave of CEF on a Pt electrode (– 0.325 V and – 0.675 V) and on a gold electrode (– 0.65 V and – 0.95 V), it can be deduced that a platinum electrode is a better catalyst for CEF electroreduction.

CONCLUSION

In conclusion, it can be said that a two step electroreduction of CEF was observed on gold and platinum electrodes as was observed on a dropping mercury electrode. The behaviour of CEF on gold and platinum electrodes can be differentiated; the Pt electrode is the better catalyst for CEF electroreduction as judged by the potentials of the reduction peaks in the first cycle. The observed adsorption, even on solid electrodes such as are gold and platinum, as well as the two step electroreduction process suggest that in the considerations of CEF reduction this phenomenon plays a great role.

И З В О Д

ЕЛЕКТРОРЕДУКЦИЈА ЦЕФЕТАМЕТА НА ЕЛЕКТРОДАМА ОД ЖИВЕ, ПЛАТИНЕ И ЗЛАТА

М. АВРАМОВ-ИВИЋ,[1] В. КАПЕТАНОВИЋ,[2] М. АЛЕКСИЋ,[2] и П. ЗУМАН[3]

[1]*ИХТМ-Центар за електрохемију, Његошева 12, 11000 Београд, Југославија,* [2]*Фармацеутски факултет, Катедра за физичку и аналитичку хемију, Војводе Степе 450, 11000 Београд, Југославија и* [3]*Универзитет Кларксон, Катедра за хемију, Потсдам, Њујорк, САД*

Редукција цефетамета на електродама од злата и платине је проучавана у слабо алкалној средини (pH 8,40) где је у претходним испитивањима на живиној електроди у току реакције уочена адсорпција антибиотика. Овај рад је посвећен испитивању утицаја адсорпције на електроредукцију цефетамета на чврстим електродама и поређењу са живом.

(Примљено 19. маја, ревидирано 12. октобра 1999)

REFERENCES

1. Wilson and Gisvold in *Textbook of Organic Medicinal and Pharmaceuticla Chemistry*, J. N. Delago, W. A. Remers (Eds.) Lippincott, Philadelphia, New York, London, Hagerstown, 1991
2. O. W. Foge, T. Lemne, D. Williams, *Principles of Medicinal Chemistry*, Lea & Febiger Book Williams & Wilkins, Baltimore, Philadelphia, A Waverly Company, 1995

3. M. Ochiai, O. Aki, A. Morimoto, T. Okada, K. Shinozaki, Y. Asahi, *J. Chem. Soc. Perkin Trans*. I (1974) 258
4. D. A. Hall, D. M. Berry, C. J. Schneider, *J. Electroanal. Chem.* **80** (1977) 155
5. F. I. Sengun, K. Ulas, I. J. Fedai, *J. Pharm. Biomed. Anal.* **3** (1985) 191
6. N. A. El. Maali, A. M. M. Ali, M. A. Grandour, *Electroanalysis* **5** (1993) 599
7. B. Ogorevc, V. Hudnik, S. Gomiscek, *Z. Fresenius Anal. Chem.* **330** (1988) 59
8. G. Bernacca, L. Nucci, F. Pergola, *Electgroanalysis* **6** (1994) 327
9. M. Aleksić, V. Kapetanović, M. Erceg, Lj. Ignjatović, D. Veselinović, *3rd Yugoslav Conference on Fundamental and Applied Aspects of Physical Chemistry*, Belgrade, Yugoslavia, September 25-27, 1996, Book of Abstracts, 221
10. E. Munoz, J.L. Avila, L. Camacho, J. E. Cosano, J. Garcia-Blanco, *J. Electroanal. Chem.* **257** (1988) 281
11. E. Munoz, J. L. Avila, L. Camacho, *J. Electroanal. Chem.* **282** (1990) 189
12. E. Munoz, L. Camacho, J. L. Avila, F. Garcia-Blanko, *Analyst* **114** (1989) 1611
13. M. Erceg, V. Kapetanović, D. Sužnejvić, D. Dumanović, *Microchemical J.* **57** (1997) 73
14. A. Ivaska, F. Nordvom, *Anal. Chim. Acta* **146** (1983) 87
15. H. Fabre, M. D. Blanchin, U. Tjaden, *Analyst* **111** (1986) 1281
16. H. Fabre, M. D. Blanchin, W. Th. Kok, *Analyst* **113** (1988) 651
17. E. Bishop, W. Hussein, *Analyst* **109** (1984) 913
18. N. Marković, M. Avramov-Ivić, N. Marinković, R. Adžić, *J. Electroanal. Chem.* **312** (1991) 115
19. M. Avramov-Ivić, J. M. Leger, B. Beden, F. Hahn, C. Lamy, *J. Electroanal. Chem.* **351** (1993) 285.