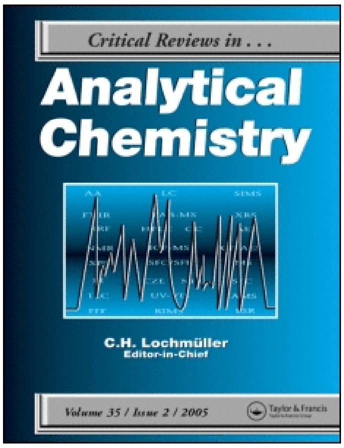

Critical Reviews in Analytical Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713400837

# Applied Polarography and Voltammetry of Organic Compounds in Practical Day-to-Day Analysis. Part 1: Applied Polarographic and Voltammetric Techniques

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**To cite this Article** Bersier, Pierre M. and Zuman, Petr(1985) 'Applied Polarography and Voltammetry of Organic Compounds in Practical Day-to-Day Analysis. Part 1: Applied Polarographic and Voltammetric Techniques', Critical Reviews in Analytical Chemistry, 16: 1, 15 — 79

**To link to this Article: DOI:** 10.1080/10408348508542784

**URL:** http://dx.doi.org/10.1080/10408348508542784

# APPLIED POLAROGRAPHY AND VOLTAMMETRY OF ORGANIC COMPOUNDS IN PRACTICAL DAY-TO-DAY ANALYSIS. PART 1: APPLIED POLAROGRAPHIC AND VOLTAMMETRIC TECHNIQUES

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## ABBREVIATIONS

| | |
|---|---|
| a.c. | alternative current (sinusoidal) polarography |
| | phase-sensitive alternative current polarography |
| a.d.p. | alternate drop differential pulse polarography |
| ASV | anodic stripping voltammetry |
| CME | chemically modified electrode |
| C.P.E. | carbon paste electrode |
| c.p.p. | constant potential pulse polarography |
| CSV | cathodic stripping voltammetry |
| CV | cyclic voltammetry |
| d.c. | direct current (polarography) |
| DASV | differential anodic stripping voltammetry |
| DCSV | differential cathodic stripping voltammetry |
| DCTA | 1,2-cyclohexanediaminetetracetic acid |
| DCV | derivative cyclic voltammetry |
| DME | dropping mercury electrode |
| d.n.p. | differential normal pulse polarography |
| d.p.p. | differential pulse polarography |
| DPSV | differential pulse stripping voltammetry |
| d.p.v. | differential pulse voltammetry |
| EGTA | ethylene glycol tetracetic acid |
| GC | gas chromatography |
| GLC | gas-liquid chromatography |
| HMDE | hanging mercury drop electrode |
| HPLC | high performance liquid chromatography |
| LPSCSV | linear potential sweep cathodic stripping voltammetry |
| LSV | linear sweep voltammetry |
| MFE | mercury film electrode |
| n.p. | normal pulse polarography |
| NTA | nitriloacetic acid |
| ODSWA | one-drop square wave analyzer |
| PSCSV | phase-selective a.c. cathodic stripping voltammetry |
| RDME | rapidly dropping mercury electrode |
| r.p.a. | reverse pulse amperometry |
| r.p.p. | reverse pulse polarography |
| SCE | saturated calomel electrode |

| | |
|---|---|
| SDC | sampled direct currect (Tast) (polarography) |
| SMDE | static mercury drop electrode |
| s.w.p. | square wave polarography |
| s.w.v. | square wave voltammetry |
| TLE | thin-layer electrode |

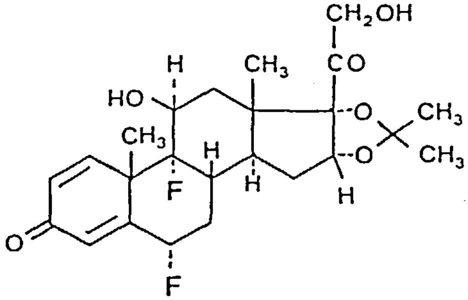
## I. INTRODUCTION

Since its discovery by Heyrovsky[1] in 1922, polarography has become one of the major techniques in analytical chemistry. Polarography was the first instrumental technique to allow quantitative determinations below $10^{-4}$ $M$. One of the main objections to polarography and voltammetry advanced by practical analysts in industry is that both techniques are purely academic; polarography is mostly encountered in basic electrochemistry courses and a glance at some of the papers published in the *Journal of Electroanalytical Chemistry* will not easily convince the reader of the direct relevance of these techniques to ordinary day-to-day analysis in an industrial control and research laboratory. There can be no doubt that in both theory and practice these two techniques are more demanding than most instrumental techniques currently used in modern laboratories. For far too long they were practiced mainly in highly specialized laboratories or institutes and thus their wide scope was simply not recognized by industry, or they were not considered adequate for simple routine work.

On the other hand, it is possible to ask why should a practical analyst consider the use of polarography or voltammetry, given the wide acceptance of photometry, spectrophotometry, or chromatography. The introduction first of gas-liquid chromatography (GLC) and then of high performance liquid chromatography (HPLC) in particular has brought a tool offering high resolution of structurally related organic compounds and sensitivities comparable or better than those of modern polarography. Such a question can best be considered using the two following examples to illustrate the usefulness (advantages and limitations) of polarographic and voltammetric techniques.

### A. Polarographic Assay of Fluocinolone Acetonide

The assay of fluocinolone acetonide (I)



in creams, gels, and ointments, using tetraethylammonium hydroxide containing 50% v/v of ethanol at pH 11 as supporting electrolyte by differential pulse polarography[2] (d.p.p.), is simple and involves just addition of an extract in methanol to the supporting electrolyte and recording of polarographic curves. Commonly used preservatives and bases in creams and gelling agents in gels do not interfere with the direct determination. Vegetable oils, synthetic esters, and fatty acids or soft paraffin when present must be removed by prior extraction with isooctane from fluocinolone acetonide ointments.

For the practical analyst the advantage of this polarographic assay is primarily that no time-consuming preparations are required, unlike in former official spectrophotometric techniques (BPC,[3] USP XIX,[4] and National Formulary[5]). However, the proposed d.p.p. procedure has the same drawback as the spectrophotometric methods in that the degradation product, if present, cannot be detected. Hence polarography will be the method of choice only in cases where the speed is essential and information concerning the degradation product is unimportant. When the latter is considered of importance, HPLC, even when more time consuming, might be preferred.

### B. Voltammetric Determination of Morphine

Differential pulse voltammetric (d.p.v.) determination of morphine in poppy straw concentrates, when carried out at a stationary glassy carbon electrode, gave results similar to those obtained by liquid and gas chromatography (cf. Reference 6, Table 2). The proposed direct d.p.v. method is rapid, requires less than 5 min to run a sample, and involves no sample preparation other than dissolving and transferring an aliquot to the supporting electrolyte consisting of a mixture of methanol and carbonate buffer. Linear calibration graphs were obtained over the range from 10 to 40 ppm. Gas chromatography (GC) involves extraction and derivatization; HPLC, while having the advantage of requiring minimal sample preparation and profiling all major alkaloids in a single run,[6] is slower than the proposed d.p.v. method, requiring about 25 min per sample.

An amperometric HPLC method described by Peterson et al.[7] for narcotic alkaloids (morphine, oxymorphone, nalorphine, naltrexone, and naloxone) detects only those alkaloids with a "catechol" structure. For codeine, 3-methoxymorphine, i.e., no signal was observed. This most probably indicates involvement of the 3-hydroxyl group of the alkaloid opiates in the electrooxidation process.

The voltammetric[6] and amperometric[7] methods do not require the derivatizations necessary for electron-capture GC, nor the long incubation and counting times needed for radioimmunoassay. The detection limits of electrochemical methods are said to be comparable to those of the latter two methods. Thus only detailed knowledge of the advantages and limitations of the techniques used for a particular problem and an objective comparison of the experimental results of the techniques available in the given laboratory can decide the ultimate choice of the most useful technique.

This review presents in Sections II and III a brief sketch of the history of polarography and in particular of organic polarography, and then points out the position of polarography and voltammetry in the industrial laboratory. Sections IV to VII discuss (with reference to predominantly organic examples) advanced polarographic and voltammetric techniques commercially available and in development (of interest for the practical analyst), conventional and commercially unavailable electrodes and cells, as well as factors that determine the usefulness of polarography and voltammetry such as applicability, sensitivity, rapidity, selectivity, and specificity.

Part 2 of this review summarizes the advantages and limitations of polarography and voltammetry in the industrial laboratory. Examples of analysis of dyes, products used in agriculture, plastics, and pharmaceuticals taken from the author's own work and from literature (with particular stress on papers published recently, during the period from 1979 to 1983) are discussed.

The review cannot be exhaustive and examples chosen are those of interest to the author in the hope that these might interest others too. Whenever possible the description is illustrated by current voltage curves, most of them recorded in the author's laboratory.

| Year | Experimental finding | |
|---|---|---|
| 1925 | electrolysis of nitrobenzene with the DME<br>- reduction potential of nitrobenzene<br>- influence of cathodic potential on adsorption of nitrobenzene | Shikata[9] |
| | researches of some organic bases (quinone) at the DME | Podrouzek |
| 1926 | reduction pot. of isovaleraldehyde | Shikata |
| 1927 | nicotinic acid | |
| 1928 | maleic/fumaric acid | Herasymento |
| (1930) | keto groups | Shikata,Tachi |
| | nitrophenols | Shikata,Watanabe |
| 1929 | camphor/fenchone | |
| 1930 | polyketones | Shikata,Tachi |
| 1931 | allylalcohol | Tachi |
| | acetaldehyde | Smoler |
| 1932 | fructose/sorbose | Heyrovsky,Smoler |
| | nicotine | Semerano |
| 1933 | new test for proteins in the presence of cobalt salts | Brdicka |
| | reduction pot. of p-amino-azobenzene | Shikata,Tachi |
| | dimethylaminobenzene | Tachi |
| 1934 | nitranilines,quinine | Shikata, Taguchi |
| | camphor | Tachi |
| | specific effects of amino-acids | Sladek,Lipschütz |

FIGURE 1A. Important steps in the development of organic polarography.

Some general aspects of history, fundamentals, electrode processes, general procedure (preliminary experiments, detailed investigations), and applicability (interferences, systematic errors) have been dealt with recently,[8] together with recommendations concerning the preparation for publication of results of such investigations.

## II. HISTORICAL REVIEW OF THE POLAROGRAPHIC TECHNIQUE AND THE POLAROGRAPHY OF ORGANIC COMPOUNDS

As an analytical technique, polarography in general and organic polarography in particular have had a checkered career. During the first period (1922 to about 1950), about 3000 papers were published and it was characterized by early acceptance as an instrumental method of trace analysis and development of organic polarography by Professor Shikata in Japan in the 1930s (Figure 1A), followed by some pioneering work of Brdicka, Mueller, Semerano, et al. Figure 1B shows "the adsorption maximum characterizing the polarization curves of aqueous solutions containing traces of nitrobenzene"[9a] published in 1925 by Heyrovsky and Shikata. The "polarogram" was recorded with the first "polarography" (photographic autoregistering machine) built at the Chemical Institute of the Charles University, Prague, by Heyrovsky.[9a]

In the late 1950s and 1960s, the technique almost disappeared from analytical laboratories even when during this period some of the classics in polarographic literature were published.[10-13] Nevertheless, it was during this period that Barker[15,18,20,22,23,25,26] and Barker et al.[14-17,19,21,24] developed the modern pulse electroanalytical methods which are the basis of modern analytical polarography and voltammetry.

The 1970s are considered "the period of the renaissance of polarographic analysis". The main reason for this renaissance[28] of polarography as a viable routine analytical technique was the recent advances in instrumental electronics making commercially

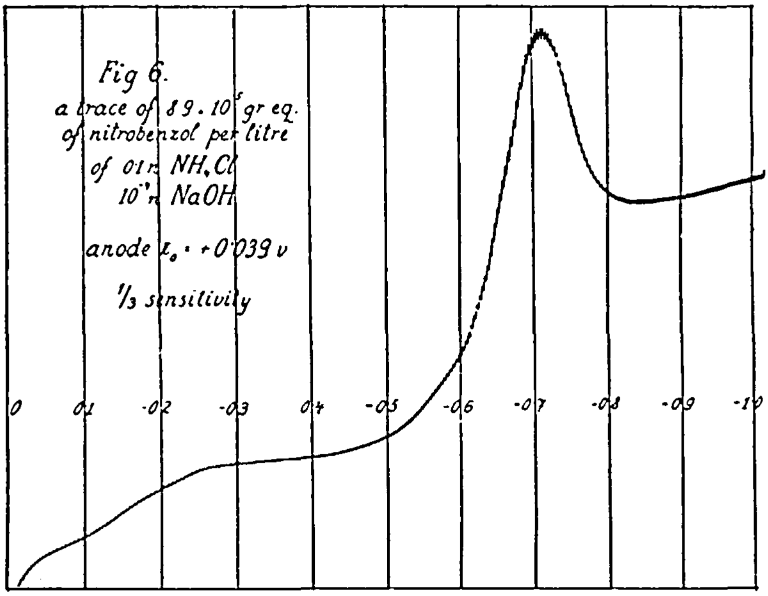


FIGURE 1B. "Polarogram"[9a] of nitrobenzene recorded in 1925 by Heyrovsky and Shikata.

available instruments[29] based on the pioneering work of Barker in England[14-27]* followed by that of Osteryoung and Parry[30,31] in the U.S. These instruments are relatively simple, very reliable (a *conditio sine qua non* for any routine work in industry), and fairly inexpensive.

The 1980s will, according to Bond,[32] come to be seen as the "decade of maturity for polarographic analysis in its modern forms". The possible replacement of the dropping mercury electrode (DME) by a static mercury drop electrode (SMDE) and the introduction of microprocessor technology[33] into many areas of instrumentations and data aquisition[34] are considered to have a possibly substantial impact on the future of the technique.[32] Among the numerous applications described, it is possible to mention studies in in vivo monitoring of catecholamines and their metabolites in freely moving rats, using a 380 Z microprocessor.[35,36] Computer-based systems provide power, flexibility for experimental control, data control, and data analysis, but often at the price of high development and overhead costs. First instruments based on the use of microprocessors have been recently developed (Metrohm, PAR, BAS) and are commercially available, but the evaluation can be proposed only after more exclusive experience. Another limiting factor often is the availability of skilled workers.[33]

Even when the use of microprocessors will simplify the supervision in industrial laboratories and diminish the costs by lesser demand on man power, the practical analyst in industry will be able to attack and solve problems only based on solid knowledge of foundations of chemical and electrochemical processes involved.

## III. SITUATION AND GOALS OF POLAROGRAPHY AND VOLTAMMETRY IN THE INDUSTRIAL ANALYTICAL LABORATORY

Over 20 years dedicated to the application and adaption of polarographic and voltammetric techniques to given problems and to the development of quantitative polarographic, voltammetric, and amperometric procedures for inorganic and organic com-

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* A list of the published works of Barker (1947 to 1975) is to be found in Reference 27.

pounds (as "main" and "secondary" methods) have shown that numerous realistic analytical problems in industry can be solved by these techniques. "Main" methods means procedures preferably used for routine work; "secondary" methods means procedures used as an alternative. In industrial analysis it is becoming increasingly desirable or even advisable to have two totally different assays. This procedure often represents the only way to ascertain the correctness of analytical data provided by a new analytical method. Meites et al.[8] state: " . . . no polarographic (or any other) analytical results (of a new procedure) should be given unless it is accompanied by one obtained by a different procedure so that the reader can form an estimate of accuracy of the procedure proposed (except, of course, in cases where no other suitable procedure exists)." "Secondary" procedures are also used for checking established anlaytical procedures such as chromatographic, spectrometric, or microbiological procedures in the organic field and X-ray fluorescence and atomic absorption spectroscopy in the inorganic field.

Another type of application of polarography and voltammetry is determination of physicochemical, thermodynamic, and kinetic parameters needed to develop industrial processes, and for elucidation of mechanisms of electrode reactions in connection with electrosynthetic problems.

In the industrial laboratory, polarography and voltammetry are thus just tools available to solve a given analytical or physicochemical problem, often used as the last resort when all other methods have failed. To cope with such problems confronting the electroanalyst, a good knowledge of Western and East European literature is indispensable. Whenever possible, published procedures are either followed directly or adapted.

As the theoretical treatments for some currently used methods (such as d.p.p.) are not yet available, it happens rather frequently that theoretical studies are carried out using several different methods. Thus direct current (d.c.) and alternative current (a.c.) polarography, as well as normal pulse polarography (n.p.) and d.p.p., were used in the study of $\alpha,\alpha,\alpha$-trifluoroacetophenone;[37] d.c. and a.c. polarography, d.p.p., and cyclic voltammetry (CV) in the study of butyrophenones;[38] and d.c. polarography, d.p.p., and linear sweep voltammetry (LSV) in that of 1-methylpyridiniumcarboxaldehydes.[39] In another type of application, whereas progestogens were determined[40] using d.p.p., the interfering substances in such determinations were identified as surfactants, based on investigation using a.c. polarography, n.p., and CV at the hanging mercury drop electrode (HMDE).

To solve industrial problems, the possibility of using all various polarographic and voltammetric techniques, including advanced techniques such as square wave, alternate drop, or reverse pulse methods, must be considered. In the author's opinion one of the reasons for the many failures of practical polarography in routine application is that many users of modern instrumental methods are rarely interested in theoretical studies. If those who develop sophisticated electrochemical methods do not illustrate their practical applications, the industrial analyst will not attempt to use them. To be able to make the best use of a given technique it is essential to understand the effect of individual parameters on the output followed. A good basic understanding of the different methods is therefore necessary. Therefore, a brief account is given here of some advanced polarographic and voltammetric techniques available for practical applications and also of those factors that determine their usefulness (applicability, sensitivity, rapidity, selectivity, and specificity).

In view of the proliferation of techniques related to polarography encountered in the literature, the reader should consult the report on the "Classification and Nomenclature of Electroanalytical Techniques".[41] This report reviews and updates the recommendations on electroanalytical classification and nomenclature made by Delahay et al.[41a]

# IV. POLAROGRAPHIC AND VOLTAMMETRIC TECHNIQUES AVAILABLE ON COMMERCIAL INSTRUMENTATION APPLIED TO ORGANIC COMPOUNDS

Numerous review articles[28,42-44] and recent monographs[45-48] give a comprehensive outline of modern polarographic and voltammetric techniques embracing most new developments. Here the discussion will be restricted to principles and possibilities of analytical applications.

Classical d.c. polarography remains the most widely used technique in initial stages of investigations of electrode processes[8,49] because of (1) renewal of the electrode surface, practically potentiostatic conditions of measurement on individual drops unaffected by electrolysis products formed at more positive or negative potentials, and (2) the independence of the limiting current of the rate of the electron transfer. For analytical applications, nevertheless, its importance is limited by the effect of charging current. For concentrations lower than about $5 \times 10^{-5}$ *M* (about 5 ppm for an organic compound with 100 mol wt), pulse methods must be used. In these methods the current is measured at the end of a voltage pulse, when the charging current has a much smaller effect (Section VII.B, Figure 22A).

## A. Pulse Mode: Limitations and Problems in Practical Use. Rapid Differential Pulse Polarography

The most commonly applied technique for most practical laboratory analysis, and even for many research applications these days, appears to be d.p.p. For example, about 80% of all papers reporting electrochemical drug analysis in 1979 to 1980 present results obtained by d.p.p. This is primarily due to the availability of simple, low-cost instruments capable of performing d.p.p. and n.p. polarography. The principles, instrumentation for, and application of pulse polarography to inorganic and organic analysis have recently been reviewed.[50-53]

The main disadvantage of d.p.p. is the relatively long time required for recording each current-voltage curve (typically 3 to 5 min), as each potential pulse is imposed only once during the drop-life and potential scan rates of the order of 50 to 200 mV/min are required.[54] Short controlled drop-times (0.1 sec) permit an increase in the scan rate, but sloping baselines are obtained and sensitivity is decreased. The practical detection limit[55] ($10^{-4}$ to $10^{-6}$ *M*) does not offer considerable improvement when compared with d.c. polarography. Shortening of the delay times between individual pulses at stationary electrodes does not influence the sensitivity and accuracy of fast scan measurements,[56-60] but such procedures suffer from the possible changes in the electrode surface in the course of the recording of the current-voltage curve. Alternate drop techniques can be applied to the rapid scan methodology as well as n.p., d.p.p., and square wave polarography in an acceptable manner.[55,61]

Recently described fast scan d.p.p. at a slowly dropping mercury electrode is said to be more sensitive than conventional d.p.p.,[54] but again can be affected by the changes in the electrode surface. A practical example for application of the fast d.p.p. is the determination of cyanuric chloride (2,4,4-chloro-1,3,5-triazine) in methanolic acetate buffer solution at pH 5.6, using a static mercury drop electrode. The detection limit is 0.2 μg/mℓ. Results obtained for the determination of triazine in air (0.01 to 14 mg/$m^{-3}$) after absorption in methanol showed good agreement with results by UV spectrophotometry.[62] The cost of the necessary equipment for fast d.p.p. using a computer-controlled analyzer was shown to be no higher than that of the equipment necessary for conventional polarography.[63]

In practical work the saving of time by decreasing the time interval needed for the recording of a current-voltage curve from minutes to seconds[55] may not play a decisive role. The experimental procedure namely consists of (1) sample preparations, (2) recording the i-E-curve, and (3) data analysis. The saving of a few minutes when compared with the time needed for the conventional d.p.p. scan will play a significant role in the overall time required for the practical analysis only in special cases.

Shortening of the time needed for deaeration by using a nebulizer (based on the Venturi effect activated by a stream of nitrogen at an input pressure of 1000 to 1500 Torr) and automatic replacement of samples in the electrolytic cell[64] seem to be much more promising approaches to an overall time saving for analysis. The oxygen removal is practically instantaneous. The step limiting the sample changeover of 20 to 40 sec is the time for sufficient sample collection in the cell.

One problem open to discussion and of interest for the practical analyst is how to evaluate the differential pulse curves. The peak current in d.p.p. is proportional to the concentration of the material in solution reacting at the electrode surface. Changes in the ohmic drop are known to affect the measured peak potential. Similarly, in agreement with theory, both peak height and peak potential depend on kinetics of the electrode process and can thus be affected by components of the solution that affect kinetics, e.g., surfactants. The possibility of measurement of area under the d.p.p. curve was considered.[65] The preference for use of the peak height or the integrated value depends on the behavior of a particular sample, mainly on the shape of the base line.

If a solid electrode is used in differential pulse voltammetry (d.p.v.) which is gradually poisoned, then the peak height will be diminished as the electrochemical rate constant decreases. A better estimation of concentration can be obtained by multiplying the peak height by the peak width.[66] This product is said to be almost independent of the electrochemical rate constant and therefore of the degree of poisoning. However, care should be exercised in using the product of the peak height and half-width in a quantitative manner, as this product is a rather complex function of both rate constant and the charge transfer coefficient.[67]

### *1. Alternate Drop Differential Pulse Polarography and Voltammetry; Constant Potential Pulse Polarography. Approaches for Correction and Suppression of Background Currents*

In the practical laboratory, one often has to work at concentrations near the detection limit of the applied technique. The practical limitation to detection is given by the magnitude and slope of the background line, rather than by a poor signal-to-noise ratio.[68]

Processes which essentially contribute to the background in polarographic techniques are charging current due to formation of the electrical double layer, faradaic reactions of impurities, and oxidation and reduction of the electrode surface, the last type being often most important when working with solid electrodes.[68] A number of techniques have been proposed to measure and carry out corrections for the background current in polarography (e.g., References 60, 69, and 70).

One of the most successful advanced techniques using the dropping mercury electrode is alternate drop differential pulse polarography (a.d.p.)[48,71] in which the background currents are compensated by substracting the current at a pulsed drop from that at a nonpulsed drop at the same moment in the drop-life and at the same potential. There is no charging current component in the measured difference, since the charging current is only a function of time and potential. Jackson et al.[73] have designed a multipurpose conversion module for PARC model 174 polarographic analyzer, which performs alternate drop pulse polarography as well as CV, derivative polarography, and constant potential, reversed polarity. Alternate drop pulse[48,61,71,74] is offered for the first time on the EC/225 from IBM. This instrument also provides constant potential pulse polarography (c.p.p.).[72,74] With solid electrodes the measurements are made on alternate pulses and the pulse is applied at alternate pulse-repetition times. Hence the name alternate pulse voltammetry.[55] The practical application of a.d.p. has not yet been generally demonstrated.

### *2. Advanced Pulse Techniques of Interest for Organic Analysis Available on Modifications of Commercial Instruments*

#### *a. Reverse Pulse Polarography (r.p.p.)*

Oldham and Parry[75] proposed in 1970 a pulse polarographic method utilizing scan reversal by which it was possible to distinguish reversible electrode processes from irreversible. The r.p.p. has features in common with the Kalousek commutator method (cf. Section IV.E) and CV r.p.p. and is superior to the classical CV in its control of the reaction conditions and its suitability for quantitative treatment.[76] Use of the pulse mode diminishes the role of the charging current which limits the usefulness of CV at fast scan rates. Scan rates of 100 V $sec^{-1}$ result in capacity currents of about 2 mA $cm^{-2}$.

This technique enables detection of intermediates and is well suited for the study of reactions poorly separated from the background as is the case for the reduction of 2-chloropyridine and 3-bromopyridine[76] and for the study of processes involving adsorption. It has also been applied to quantitative treatment of second-order chemical reactions following reversible electron transfer. Dimerization of *N*-methyl-2-carbomethoxypyridinium in acetonitrile with 0.25 $M$ $LiClO_4$ is an example.[77] For recent applications of r.p.p. the reader is referred to References 78 to 81.

Reverse pulse amperometry (r.p.a.) was employed for the determination of reducible compounds producing species which can be oxidized at potentials more positive than those of reduction of oxygen. It yields anodic currents which can be measured, e.g., for flow injection analysis[82] or chromatography with an indicator electrode in a flowing system from which the oxygen needs not to be removed. Thus it is possible to measure concentrations of ferricyanide, NAD, chlorpromazine, and benzoquinone by measuring anodic currents corresponding to oxidation of ferrocyanide, NADH, dihydrochlorpromazine, or hydroquinone in solutions saturated with oxygen. Flow injection analysis enabled, e.g., analysis of 1 to 6 $\mu M$ solutions of chlorpromazine (corresponding to 29 to 174 ng in 83 $\mu l$ of the injection fluid).

The r.p.p. technique using a Tacussel PR 64 and a modified PAR 174 polarographic analyzer[82a] has been used successfully in the author's laboratory for various practical analyses. Figure 2 shows pulse polarograms recorded with the Tacussel instrument PRG 4.

#### *b. Differential Normal Pulse Polarography (d.n.p.)*

This technique is based upon application of a double potential pulse of short duration and the differential display of sampled chronoamperometric responses.[83-85] It is thus a hybrid of d.p.p. and n.p.p.[86] It retains advantages of conventional pulse techniques: high current sensitivity due to short pulse widths and excellent discrimination against charging currents. For irreversible systems, d.n.p. can be of an order of magnitude more sensitive than d.p.p. and is of approximately the same sensitivity for reversible systems. It also finds applications in the study of reactions at solid electrodes and in cases of electrode passivation or filming which often forms a very serious problem in organic voltammetry.

### B. Square Wave Polarography and Square Wave Voltammetry*

Square wave polarography[14,87-90] (s.w.p.) was first proposed by Barker and Jenkins[14] in 1952. It was very successful in inorganic trace analysis in the 1960s, permitting con-

* By definition, polarography = registration of a current-potential curve (i-E curve) at a dropping, usually the dropping mercury electrode (DME); voltammetry = registration of a current-potential curve at a solid, stationary, or rotating microelectrode (Pt, Au, C, etc.).

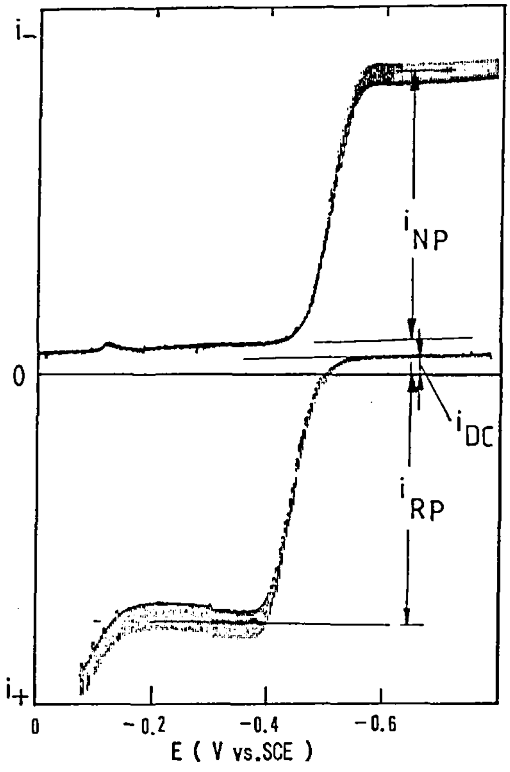

FIGURE 2. Normal pulse (a) and reverse pulse (b) polarogram of anthraquinone sodium disulfonate (1.5 mg m$l^{-1}$ Stretford solution). Scan rate 20 mV sec$^{-1}$; drop time 1 sec; delay (T) 8 sec; pulse duration 5 msec.

centrations as low as $5 \times 10^{-8}$ *M* to be determined. Furthermore, anodic stripping voltammetry (ASV) on a hanging mercury drop combined with s.w.p. has been developed.[15,91,92] In the first application of s.w.p. to organic systems,[17] the adsorption-description "waves" of octylalcohol were studied. For the first-generation instruments the application in the organic field remained limited; an exception was the estimate of approximate molecular weights of polymers.[93,94] The lack of availability of economical instruments hindered acceptance of the method for widespread application for routine analysis in the 1960s and 1970s. A modern instrument providing the s.w.p. mode is the Metrohm 646 VA-Processor.

The major advantage of s.w.p. in its modern form[95-97] is that it is faster than d.p.p., as a complete potential scan is accomplished on each mercury drop. Speed of square wave voltammetry (s.w.v.) methods is very useful when solid electrodes are used. Besides giving analytical information, s.w.v. can be used for studies of the kinetics of electrode reactions and mechanisms.[98]

The ability to carry out a fast complete scan gives s.w.v. potential for use as a selective and sensitive detector for HPLC for organic substances that can be oxidized or reduced.[98,99] The time for a complete voltage scan is short (2 sec) in comparison with the elution time and this allows resolution electrochemically of species not resolved chromatographically. The peak potential provides an additional parameter for compound identification.[98] An example of such application is the rapid-scan s.w.v. detector used for HPLC for the determination of *N*-nitrosoproline and *N*-nitrosodiethanolamine.[99] The cycle time in this experiment was 2 sec and the chromatopolarogram is obtained from 102 consecutive scans.

s.w.v. and s.w.p. also offer the advantage of being more sensitive than d.p.p., both for reversible and irreversible systems. Thus s.w.p., for instance, is superior to d.p.p. for the determination of EDTA, 1,2-cyclohexanediaminetetracetic acid (DCTA), (ethylene glycol) *bis* ($\beta$-aminoethyl ether) *N,N,N′, N′*-tetracetic acid (EGTA), and nitrilotriacetic acid (NTA).[100] The technique used in this special case was one-drop s.w.p.[101] The detection limits were found to be $7 \times 10^{-8}$, $7 \times 10^{-8}$, $5 \times 10^{-8}$, and $2 \times 10^{-7}$ *M*, respectively.

From the point of view of practical analysis, attention should be paid to spurious peaks[102] observed in rapid-scan s.w.p. The height of the spurious peaks can correspond to faradaic waves in the $10^{-7}$ to $10^{-8}$ *M* concentration range. The judicious choice of instrument parameters (such as flow rate of the mercury, delay time, and initial potential) ensures that in most practical applications this interference can be avoided.[102] A practical application of s.w.p. is the routine identification of penicillins, 6-aminopenicillanic acid, and semisynthetic penicillins in drugs and urine.[103]

The application of the first-generation pulse techniques (in particular of d.p.p., mentioned above) especially in pharmaceutical, clinical, and environmental analysis[104,105] was enabled by availability of these modes in commercial instruments. The success of the second-generation pulse techniques (such as d.n.p. and r.p.p.) as well as s.w.v. in industrial laboratories will depend on availability of inexpensive commercial instruments.[42]

Other methods, briefly discussed in this section, such as LSV, CV, a.c. polarography, and Kalousek commutator, are primarily useful in mechanistic studies, in identification of electrolysis products, role of chemical reactions, and adsorption. a.c. polarography is sometimes promoted as an analytical method, but its strong dependence on the kinetics of the electrode process and its marked sensitivity to adsorption phenomena limit its practical application for analysis of organic samples.

### C. Linear-Sweep, Cyclic Voltammetry: Applications to Derivative Techniques

The growing appreciation of electrochemical methods as complements to spectroscopic techniques has "greatly increased the use of such methods as CV and LSV in organic and inorganic chemical investigations."[106,107] CV is important for studies of redox rates and mechanisms, which are often of interest to synthetic organic chemists.

In special cases LSV (and even more rarely, CV) can be used for analytical purposes. For example, oxidation of morphine at a graphite or platinum electrode can be used for its determination in the range of $6 \times 10^{-5}$ to $1 \times 10^{-3}$ *M*. It can be used for a rapid estimate of morphine content in crude morphine and in plant material in the presence of minor alkaloids.[108] The method is claimed to be reproducible, but the necessity to repeat recording of the calibration curve is a distinct disadvantage.

The analytical usefulness of LSV and CV is often overestimated. The chief limitation is due to the fact that the current for any non-Nernstian process depends on the value of $\alpha n_a$ for the process. Unexpected and therefore uncontrollable presence of traces of surface-active materials (ubiquitous in organic electrochemistry in the chemicals used, or even in the water used — especially obtained from mixed-bed ion exchange) can often substantially alter the $\alpha n_a$.[8]

The simultaneous determination of a species in the presence of another more positively reduced or more negatively oxidized (Figure 3) presents great difficulties in LSV because the baseline current arising from the first process has to be extrapolated.[48] The quantitative use of LSV and CV is therefore largely restricted to the analysis of samples that contain only one single electroactive species, or two or more if the peak potential for the substance of interest differs substantially.

The use of derivative mode of LSV was claimed[109-112] to improve the sensitivity and resolution of adjacent peaks (cf. Figure 3b). However, a word of caution is needed.

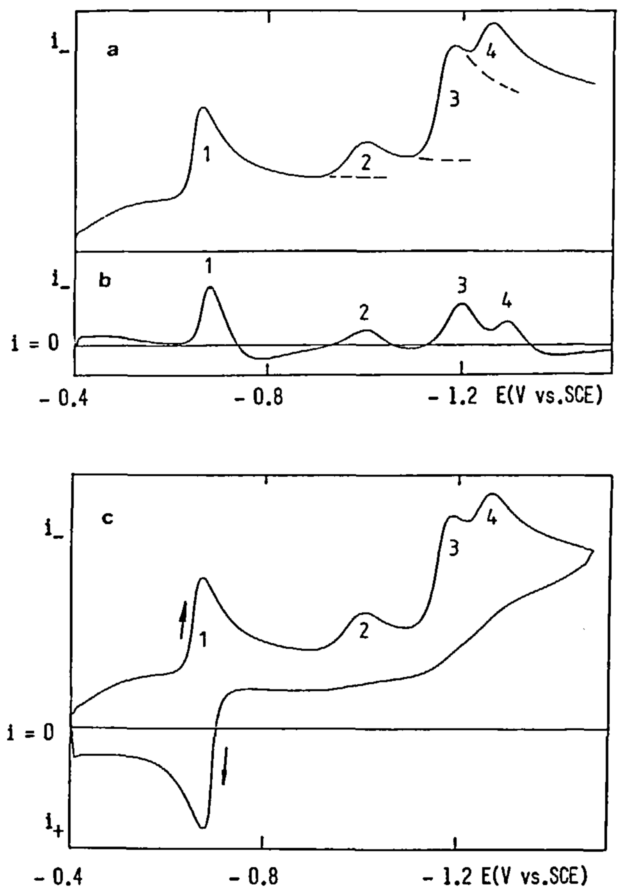

FIGURE 3. (a) Linear sweep voltammogram of a mixture of (1) 15 $\mu g$ anthraquinone, (2) 15.15 $\mu g$ dianthrone, (3) 24.24 $\mu g$ oxanthrone, (4) 15.06 $\mu g$ anthrone in 1 $ml$ 0.05 $M$ tetraethylammonium perchlorate in methanol. Measured at the HMDE, scan = 250 mV $sec^{-1}$. (b) Derivative linear potential sweep voltammogram. (c) Cyclic voltammogram (CV).

Considerable discretion should be employed in deciding when a derivative plot will prove advantageous if the electrode mechanism is complex and not well understood.[48]

### D. Sinusoidal A.C. Polarography (Fundamental and Second Harmonic)

The principles of a.c. polarography and its analytical applications have recently been discussed.[48,113] In the most commonly used phase-selective a.c. polarography the background current and noise caused by capacitance effects can be diminished by phase-sensitive measurement of the in-phase component of the alternating current. This mode is suitable for application of low detection limits.[114] The symmetrical peaks (summits) allow enhancement of selectivity. Furthermore, the possibility of measuring the change in the mercury drop capacity opens the way to determining adsorbed but nonelectroactive species (see Section IV.D.2). An example of practical use of a.c. polarography is the analysis of a commercial multivitamin drageé. Out of the 37 substances (Table 1), 25 are amenable to polarographic or voltammetric analysis.

The vitamin $K_3$ contents found by UV assays of such preparation to be significantly lower than the values indicated by the manufacturer were corroborated by d.p.p. Be-

Table 1
COMPOSITION OF A COMMERCIAL MULTIVITAMIN DRAGEÉ

| | | | |
|---|---|---|---|
| Core | | | |
| Vitamin | | | |
| A palmitate | 5000 IE | Fe-fumarate | 60.0 mg |
| $D_2$ | 500 | KJ | 0.01 |
| $B_1$ | 3.0 mg | $CuSO_4 \cdot 5H_2O$ | 0.5 |
| $B_2$ | 3.0 | $CaF_2$ | 0.01 |
| $B_6$ | 1.0 | $MgCO_3$ | 0.5 |
| $B_{12}$ | 15.0 | $MnSO_4 \cdot H_2O$ | 0.1 |
| E | 1.0 | $(NH_4)MoO_4 \cdot 4H_2O$ | 0.02 |
| C | 50.0 | $K_2SO_4$ | 0.75 |
| $K_3$ | 0.5 | $ZnSO_4 \cdot 7H_2O$ | 0.1 |
| Calcium panthothenate | 3.0 | Mg-stearate | 1.0 |
| Nicotinamide (vit. PP) | 20.0 | Gelatin | 2.4 |
| Folic acid | 0.5 | Lactose | 208.6 |
| Ca-lactate ($5H_2O$) | 20.0 | Talc | 10.0 |
| Envelope | | | |
| Polymethacrylic acid | 10.8 mg | Saccharose | 230.1 mg |
| Cromophore EL | 0.2 | Hard paraffin | Traces |
| Lauric acid | 0.8 | Dyes | 0.02 mg |
| Arabic gum | 2.4 | Tartrazine | |
| Starch | 9.0 | Ponceau 4R | |
| Talc | 16.0 | Brilliant black | |

sides the contents of vitamin $K_3$, vitamins C, $B_2$, folic acid, and nicotinamide could be monitored simultaneously by a proper choice of the instrumental mode and media. Thus the waves of vitamin $K_3$ ($E_p = -65$ mV vs. saturated calomel electrode [SCE]) and folic acid ($E_p = -550$ mV vs. SCE) can be made to appear merely by changing the mode from d.p.p. (Figure 4A) to a.c. (Figure 4B).

In particular, the behavior of folic acid is worth noting. The a.c. wave of this compound is about 30 times higher than d.p.p. when recorded at comparable sensitivities[115] (Figure 5). This behavior was attributed[116] to adsorption processes. The a.c. technique thus seems to be the best for a quantitative assay of folic acid, although cathodic[117,118] and anodic[119] d.c. and d.p.p. procedures have been described recently. As the suppression of the charging current is hardly ever complete, the sensitivity of a.c. polarography is still limited by the magnitude of the background or charging current.[48]

For irreversible electrode processes, solution conditions can be very critical and must be strictly controlled. For many organic electrode processes in aqueous media, protonation or deprotonation of the reactant or product is involved, and buffering of solutions is required.

The use of nonaqueous solvents eliminates or decreases the influence of coupled chemical reactions on the first electron uptake for many organic systems. Thus a.c. polarography often offers more advantages in aprotic media, as was shown for a wide range of pharmaceuticals.[120-122] An example is the assay of reserpine by a.c. in an aprotic solvent system.[123] Reserpine can be determined at $1 \times 10^{-6}$ *M* by either a.c. polarography or d.p.p. and the results of such polarographic and the rather tedious United States Pharmacopeia (USP) assays of synthetically formulated reserpine tablets compare favorably.[124,125] The sensitivity of polarographic method is adequate for content uniformity studies.

It is important to stress from the practical analyst's point of view that although a.c. methods are often regarded as applicable only to reversible electrochemical reactions, this is not always the case. Measurable a.c. waves can be found for even completely

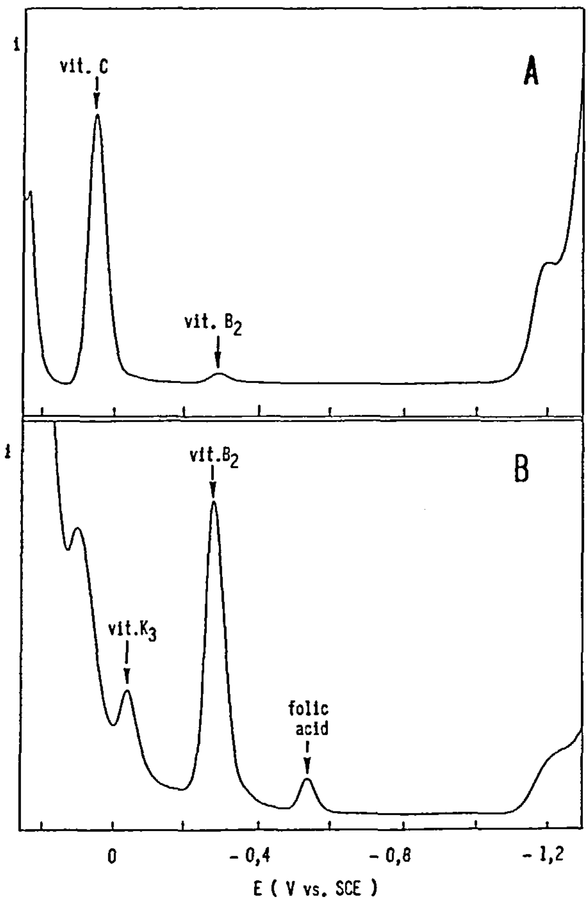

FIGURE 4. Choice of the polarographic technique. Assay of a multivitamin drageé (see Table 1) in sodium acetate buffer, pH 4.4 (A) d.p.p. mode: drop time 1 sec; scan rate 2 mV $sec^{-1}$; pulse amplitude −10 mV. (B) a.c. mode: scan rate 2 mV $sec^{-1}$; drop time 1 sec; amplitude 10 mV pp; frequency 200 Hz.

irreversible processes, although the sensitivity of such procedures is lower than those for reversible reactions (cf. Figures 6 and 7 and also Reference 113). In addition to fundamental-harmonic, second-harmonic a.c. polarography has also been applied to the analysis of organic systems (cf. Figure 7 and also References 123 and 124).

Among presently available instruments which provide a.c.-fundamental and second-fundamental a.c. modes are those manufactured by Tacussel (PRG 3), Metrohm Polarecord (E 506), Amel (Model 471), PAR (174 A with 174/50 a.c. Polarographic Analyzer interface and lock-in amplifier), and Sargent-Welsh (Model 5001 Polarograph).

## E. Kalousek Mode

Kalousek polarography[126-129] (mentioned above in connection with r.p.p.) is a large-amplitude square-wave technique in which the recorded current results in part from reoxidation of the reduction products at the dropping mercury electrode; it is potentially capable of resolving reversible and irreversible processes and may be applicable to systems that cannot be resolved by other techniques[129] except r.p.p. Even when computerized versions of instruments enabling Kalousek polarography have been described,[126] the only commercial instrument which can be used for recording of curves of electrolysis products is the Metrohm Polarecord 506.

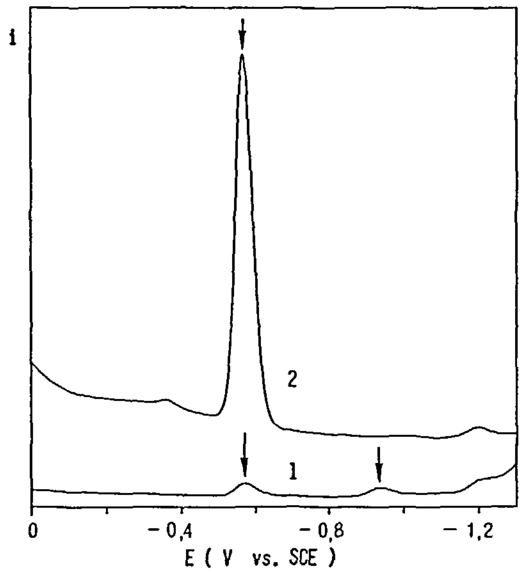

FIGURE 5. Differential pulse (1) and a.c. (2) polarogram of folic acid in placebo in 0.1 *M* sodium acetate, pH 4.5. d.p.p.: drop time 1 sec; scan rate 2 mV sec$^{-1}$; drop time 1 sec; amplitude 10 mV pp; frequency 200 Hz.

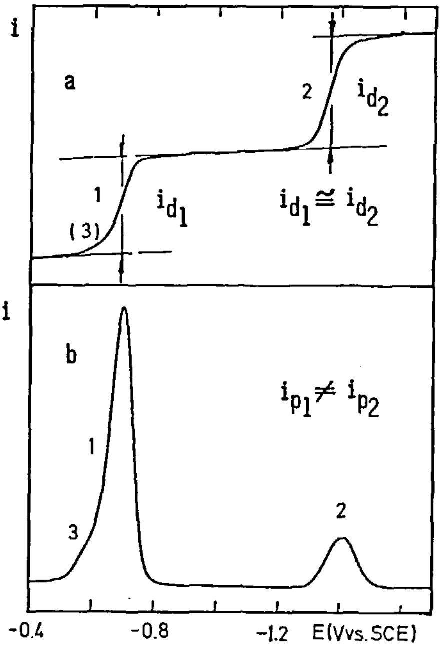

FIGURE 6. Comparison of the height of the reversible reduction step of anthraquinone (1) and the irreversible wave of anthrone (2), recorded by sampled d.c. polarography (a) and phase-sensitive a.c. polarography (b). (3) Unidentified impurity. (1) Anthraquinone 50.5 μg, (2) 52.6 μg anthrone in 1 m*l* 0.05 *M* tetraethylammonium percholorate in methanol. Recorded with PAR 174A/174-50 lock-in PAR 124.

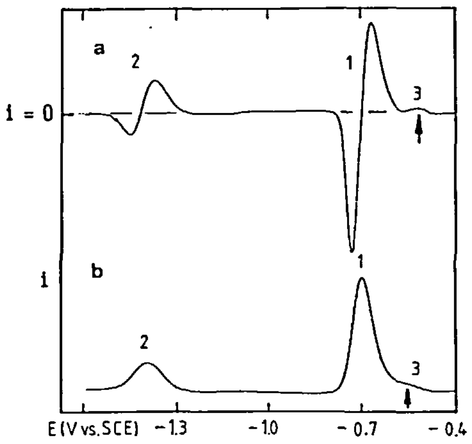

FIGURE 7. Comparison of the second-harmonic phase-sensitive a.c. polarogram (a) and the phase-sensitive polarogram (b) of anthraquinone (1) and anthrone (2). The better resolution of the second-harmonic record is clearly seen for wave (3) of the unidentified impurity. (a) Sensitivity = $4 \times 10^{-8}$ A $mm^{-1}$. (b) Sensitivity = $4 \times 10^{-7}$ A $mm^{-1}$. Recorded with Metrohm, Polarecord 506.

Few practical quantitative applications in the organic field have been published, such as studies of the adsorption-desorption phenomena of organic substances such as tri-*n*-butylphosphate, thymol, and sodium laurylsulfate[130] and evaluation of surfactant activity of polluted seawater.[131,132]

## V. WORKING ELECTRODES AND CELLS

### A. Conventional (Commercially Available) Working Electrodes

Polarography became a widely used analytical tool with the application of the dropping mercury electrode (DME) by Heyrovsky[1] in 1922. Besides the classical DME which is used today mostly in the vertical arrangement with drop-time control, numerous other mercury electrodes were developed, such as rapidly dropping DME, DME with long drop times (60 to 80 sec), as well as mercury electrodes with constant surface area such as sessile drop, hanging drop, mercury pool and streaming mercury electrodes, mercury-coated platinum or mercury-covered graphite (Hg-film) electrodes,[133,134] etc. Properties and preparation of these electrodes have been reviewed.[135]

Due to the high hydrogen overvoltage on mercury the accessible voltage range for reductions at the DME is relatively wide (∼ −2.7 V vs. SCE). The scope of reduction at the DME is roughly parallel to those substances reduced by metallic sodium.[136] On the other hand, the number of compounds oxidizable at the DME is limited by the fact that mercury, of which the electrode is made, is dissolved. Under optimum conditions +0.4 V vs. SCE can be achieved, which makes it possible to oxidize only strong reducing agents such as hydroquinones, and their nitrogen analogs, some leukodyestuffs, enediols, phenylhydroxylamino derivatives, etc. For less easily oxidizable substances, solid electrodes must be used, with all the intricacies caused by the little defined surface of such electrodes.[137]

Solid electrodes have gained greater importance in analytical voltammetry over the last 10 to 15 years, and more recently as electrometric sensors used in HPLC. The monograph *Electrochemistry at Solid Electrodes*[138] provides an excellent comprehensive discussion of the use of solid electrodes. The particularly important aspect of pretreatment of solid electrodes has recently been reviewed.[139]

### *1. The Static Mercury Drop Electrode (SMDE)*

The SMDE incorporates a mercury reservoir and a capillary through which the mercury flows to form a drop. A built-in valve allows the mercury flow to be stopped at selected time intervals to produce a stationary rather than a growing drop. The stationary drop is held for a preset period before the drop is mechanically dislodged. The SMDE thus retains the advantages of the conventional DME, e.g., renewable electrode of constant size, reproducible surface characteristics, etc. The use of widebore capillary by PAR (Model 303), for instance, allows relatively large drop areas to grow very rapidly. Other commercially available systems are manufactured by Metrohm (stand VA 663 and 647) and by Laboratorní Přistroje[43] (Tesla, Prague).

The author's policy has always been to change the capillary electrode at the slightest mechanical trouble, a policy which must be revised when using certain SMDE capillaries, due to their very high price. Our experience with the SMDE reveals an improved, flatter baseline. As the electrode is prone to many disturbances, especially in aprotic systems, close control is necessary.

Literature on this novel electrode[33,140-143] provides a critical evaluation for the practical analyst, though the number of practical applications is still very limited. The analytical performance and sensitivity limits of d.c., n.p., and d.p.p. with the SMDE and the DME have been compared.[144] Bond et al.[145] presented a simple theoretical interpretation of d.p.p. at the SMDE for a reversible electrode process, and more recently[146] a number of models using a modified Cotterell equation and digital simulation to describe the function of the SMDE. The valve-controlled operation of the electrode creates a complex hydrodynamics problem. Oscillations observed in the current during the growth period are in sharp contrast to results expected from simple gravity-controlled drop growth ($t^{1/6}$); apparently the mercury drop does not immediately stop growing after the selenoid closes the valve. According to this study the simplest and most expedient approach would be to use a potential time wave form in which the potential of interest is not applied until after drop growth and subsequent hydrodynamics have ceased.[146] Experimental d.c.-limiting currents at the SMDE were shown to differ from those calculated on the basis of spherical diffusion by about 10% due to capillary shielding effects.[80]

The essential problem with the SMDE is that the mode of transport has not been dealt with yet in detail* theoretically.[191] Users should be warned not to use expressions and diagnostic tools developed for DME directly for curves obtained with SMDE.[622]

## B. Noncommercially Available Working Electrodes and Cells

Replacement of mercury as electrode metal is of importance particularly for the study and use of oxidation processes because of the limited range of mercury electrodes in the region of positive potentials. In spite of considerable complications, resulting mainly from surface oxidation of the metal, platinum electrodes are often used. The main thrust in applications involving electrooxidation is, nevertheless, towards the use of various forms of carbon electrodes. Carbon paste electrodes, in which carbon particles are dispersed in organic materials, are perhaps mostly used for oxidations of amines, phenols, and other organic compounds.[138,147-150] Recently, it has been demonstrated that species which are slightly soluble in polar solvents can be incorporated into the electrode when the electroactive compound is mixed either with the carbon binder (paste) or with the carbon powder. Such "incorporated paste electrodes" or "carbon paste electroactive electrodes"[150] were studied for quinoid, organometallic, and other compounds,[151-156] and were successfully used[157] for the determination of oxidation-

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* A model describing the combined effects of electrochemical kinetics, ohmic potential drop, and mass transfer for a metal deposition reaction at the SMDE was presented recently.[164]

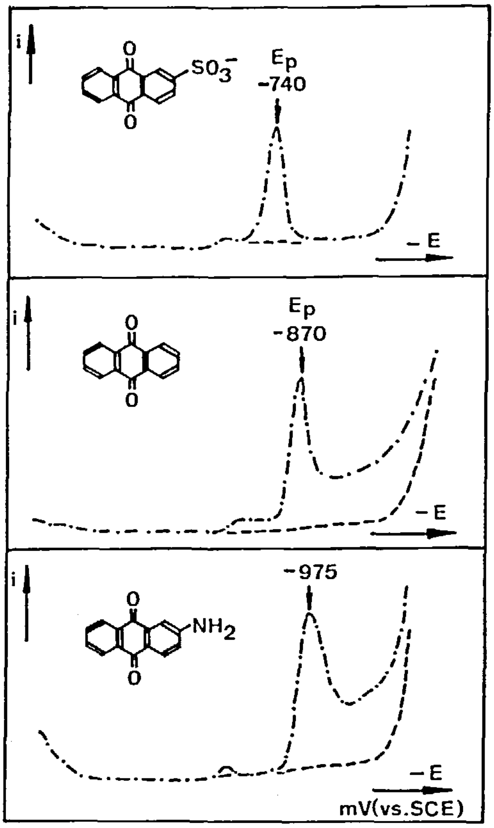


FIGURE 8. Voltammograms of different anthraquinones incorporated in a carbon-paste electrode, recorded in 1.25 *M* sodium hydroxide at 23°C.

reduction potentials of slightly soluble anthraquinones used as additives in pulping process (Figure 8). Quantitative aspects of such electrodes have not been investigated for organic species. Similarly, chemically modified electrodes with functionalized surface[158-160b] or thin-layer film electrodes (where quinoid compounds[161] or 3,4-chlorofluoroaniline[162] are applied as a film on pyrolytic graphite or carbon paste, respectively) are as yet of little practical importance.

Any attempt to summarize the trends in development of electrolytic cells used in polarography and voltammetry is thwarted by their large number. It has been said that each electrochemist and analytical chemist working in these areas designed at least one cell. Consequently, numerous cells both for general purposes or special use have been described; however, real differences among them are small and very often unrelated to essentials.[163] Most commonly used are cells provided by manufacturers of polarographic equipment. The reader is referred to a review article[163] and to monographs on polarography.[165,166] Here only two cells for special purposes will be discussed.

### *1. Thin-Layer Cells*

Theory[167-169] and applications[167-169] of thin-layer cell techniques are well documented. A variety of electrode and cell designs have been described.[168] To minimize ohmic polarization which limits the applicability to routine work because of its distortion effect on electrochemical response curves, porous-boundary (porous Vycor glass) separators[168,170] and more recently Nafion separators have been used.[171,172] The follow-

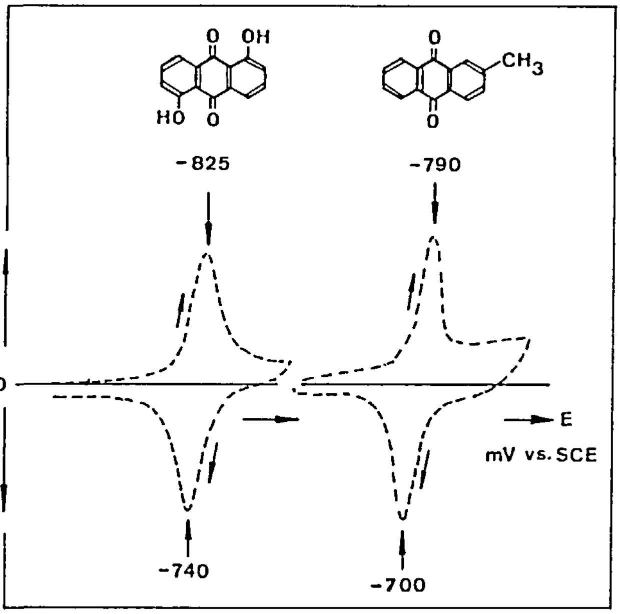


FIGURE 9. Thin-layer voltammograms of the soluble 1,5-dihydroxyanthraquinone and the sparingly solved 2-methylanthraquinone, recorded in 1 *M* sodium hydroxide at 23°C (layer = 35 μm).

ing examples illustrate recent practical applications in pharmaceutical analysis and for the study of sparingly soluble compounds.

The advantage of combining small volume capability of the thin-layer cell with the low detection limit of d.p.p. has been demonstrated on a 60-μℓ sample of the drug diazepam. A linear calibration plot was found for the concentration range from 1 to 60 μg $\ell^{-1}$. The detection limit of 0.1 μg m$\ell^{-1}$ is lower than the value 0.4 μg m$\ell^{-1}$ reported for d.p.p.[173] A thin-layer cell of 23-μℓ capacity with a wax-impregnated graphite electrode can be used[174] for rapid determination of chlorpromazine in plasma and urine. No sample pretreatment is necessary for the urine assay for chlorpromazine concentrations in the range from $4 \times 10^{-8}$ to $2.4 \times 10^{-4}$ *M*. Direct determination of chlorpromazine is also feasible in plasma over the range from $2.4 \times 10^{-5}$ to $4.8 \times 10^{-4}$ *M* with 89% recovery. The procedure for plasma and urine requires only 2 min per determination. In pure solutions, the observed detection limit of $5 \times 10^{-9}$ *M* suggests that chlorpromazine was being concentrated at the wax-impregnated graphite electrode either by adsorption at the electrode interface or by extraction into the wax, or both.[175] Results of d.p.v. and chronocoulometric measurements are consistent with a preconcentration step. Various designs of thin-layer cells are used as sensors for HPLC. In our laboratory[157,176] a modified thin-layer cell was used[177] to determine the reduction-oxidation potentials of soluble and sparingly solved quinoid compounds (Figure 9). The behavior of dissolved or finely suspended products was followed in a 35-μm layer of 1 *M* NaOH.

### *2. Pressure Cell for Voltammetric Measurements of Pulping Additives Under Pulping Conditions In Situ at 150°C*

Since at room temperature most of the substances participating as additives in the pulping process are only slightly soluble in strongly alkaline solutions, it was necessary to develop a cell[157,176] which would be able to carry out voltammetric measurements in 1 *M* NaOH at 150°C at pressures up to 50 bars (Figure 10; consult Reference 157 for

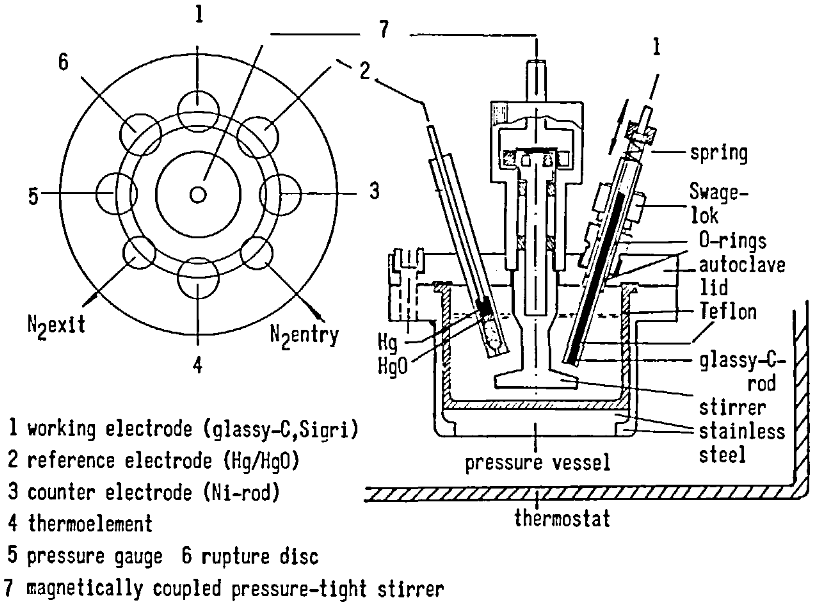


FIGURE 10. Pressure cell used for voltammetric measurements.

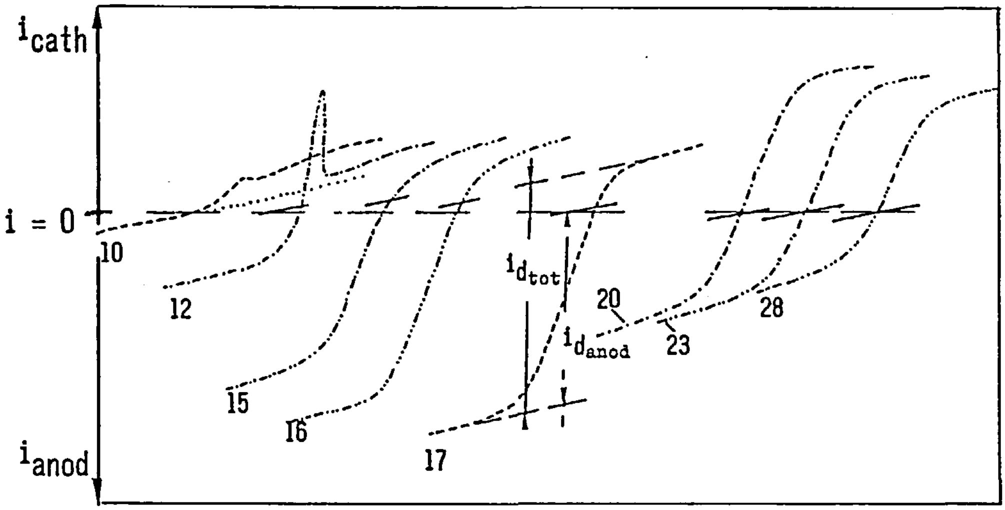


FIGURE 11. Voltammograms of anthraquinone measured *in situ* in 1 *M* NaOH containing spruce chips at different cooking times and different cooking temperatures. Shown are 8 out of 30 curves run for one cooking experiment. Curve 10 = measured after 46 min at 18°C; 12 = 54 min at 42°C; 15 = 63 min at 114°C; 16 = 66 min at 140°C; 17 = 68 min at 150°C; 20 = 78 min at 150°C; 23 = 96 min at 150°C; 28 = 126 min at 150°C. (.......) 1 *M* NaOH + spruce chips, meaured at 18°C.

construction details). Examples of current-voltage curves obtained with d.c. polarography in 1 *M* NaOH containing spruce chips and anthraquinone after varying cooking time and at varying temperatures are shown in Figure 11.

Table 2
POLAROGRAPHIC
ELECTROLYTIC CURRENTS[183]

| Current | Symbol | Concentration dependence |
|---|---|---|
| Diffusion | $i_d$ | k.c |
| Kinetic | $i_k$ | k.c |
| Catalytic | $i_{cat}$ | lim[a] |
| Adsorption | $i_{ad}$ | lim[a] |

[a] The current reaches a limiting value with increasing concentration.

## VI. CHOICE OF CURRENTS IN APPLIED ORGANIC POLAROGRAPHY AND VOLTAMMETRY

The scope of polarography depends not only on the ability of various available modes (d.c., a.c., pulse, etc.) to apply to different groups or individual compounds, but also on the possibility of using electrochemical processes other than simple oxidation or reduction. The response (current) measured in polarographic and voltammetric techniques is most often governed by diffusion ($i_d$). Nevertheless, in some cases it can be limited by the rate of a chemical reaction (kinetic currents, $i_k$), or of a catalytic process (catalytic currents, $i_{cat}$), or depend on adsorption currents ($i_{ad}$) (Table 2). For a detailed discussion of individual types of currents and diagnostic tools used for their distinguishing, the reader is referred to monographs.[10-12,45,47,48,179,180]

In most cases, a given substance will give one or two types of currents. Sometimes, as in the case of actinomycin,[181] the compound can act at the same time as an electroactive species and as a surfactant. Presence of various types of currents (and importance of their distinguishing) can be demonstrated on the class of compounds denoted as biopolymers[182] which can yield:

1. *Reduction* currents are observed, e.g., for nucleic acids in which reducible sites are represented by adenine and cytosine residues; for proteins containing cystine residues; and for conjugated proteins containing a reducible nonprotein group.
2. *Catalytic* currents are yielded by proteins containing cystine or cysteine residues in ammoniacal cobalt solutions, which give rise to catalytic hydrogen evolution.
3. *Adsorption* currents (tensammetric waves) are yielded by natural and synthetic polynucleotides, polysaccharides, and polypeptides.

The following examples will serve to demonstrate the possibility of using cathodic and anodic diffusion, kinetic, catalytic, and adsorption type currents for practical analytical applications.

### A. Choice of Currents for Analysis

Most commonly exploited are diffusion-controlled reduction and oxidation currents using a mercury electrode (dropping or stationary) for the cathodic processes or solid electrodes (noble metals, carbon, graphite, etc.) mainly for anodic ones. Diffusion currents are usually a linear function of the concentration of the substance analyzed over a large concentration range. In practical analysis one should always try to find out which type of process, cathodic or anodic, is more advantageous for the solution of a given problem.

### *1. Cathodic or Anodic Process*

### *a. Assay of Folic Acid: Cathodic Process*

A fast d.c. polarographic method for the determination of folic acid, nicotinamide, and riboflavin (vitamin $B_2$) in polyvitamin tablets was reported.[118] The method is aimed at routine checks, without separation of the other components of the tablets. The content of the active ingredient was measured using a DME in the turbid solution after treatment of the powdered preparation with alkaline sodium citrate solution at pH 12.

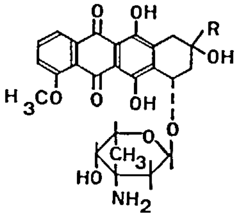
### *b. Assay of Folic Acid: Anodic Process*

Differential pulse voltammetry at a glassy carbon electrode can be applied to the determination of folic acid, pyridoxine hydrochloric acid, and ascorbic acid based on their oxidations* in multivitamin preparations.[119] The results obtained by voltammetry compared favorably in terms of accuracy and precision with official methods. The differential pulse voltammograms of folic acid in a dibasic potassium phosphate medium with $E_p = +0.63$ V vs. SCE allowed rapid reproducible determination of this vitamin by a standard addition procedure. The method is simple, with sample manipulation kept to a minimum, and therefore is accepted as an alternative to the USP 20th revision. This example shows, depending on conditions, that determination of folic acid in formulated forms can be carried out using its reduction or oxidation.

### *c. Assay of Adriamycin: Compound with Two Electroactive Sites*

Anthracycline antibiotics contain two electroactive sites: a reducible quinone group and an oxidizable hydroquinone center.

Adriamycin is a highly effective antineoplastic agent against human solid tumors, lymphomas, and acute leukemias.[184] Analytical methods for the determination of these compounds and metabolites[185] in body fluids and tissues can be based either on their reduction or their oxidation.



Reduction of the quinone group — To determine the total concentration of adriamycin in plasma[184] using a fast d.p.p. method, the current-voltage curve was recorded after introduction of the DME into a deaerated, untreated plasma sample. *N*-Amylalcohol was added to prevent frothing and thus loss of sample. A linear relationship was found for the peak current over a range from $8 \times 10^{-6}$ to $1 \times 10^{-3}$ *M*. The presence of plasma medium components or of 11 different antineoplastic agents used in combination with adriamycin does not influence the single, well-formed d.p.p. peak. The detection limit of the d.p.p. procedure is about 400 ng $m\ell^{-1}$ compared to 20 ng $m\ell^{-1}$ for the fluorimetric and 1 ng $m\ell^{-1}$ for the radioimmunoassay, but the latter methods require considerable sample handling. The d.p.p. method is nondestructive so the plasma samples can be recovered after the d.p.p. assay and subsequently used for other clinical tests. The method does not differentiate between the parent drug and metabolites such as aglycone, adriamycinol, adriamycinol aglycone, and deoxyadriamycin. When spec-

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* The problem with d.p.p. is that the shape of peaks does not indicate whether anodic or cathodic process occurs.

ificity is not required, no sample preparation is needed as mentioned above and the measurement can be completed in less than 5 min.[184]

Oxidation of the hydroquinone group — A well-shaped anodic differential pulse wave was observed at carbon paste electrodes at concentrations as low as 1 × $10^{-8}$ *M*.[185] Due to adsorption effects of the adriamycin, no linear dependence was found over the range of $10^{-4}$ to $10^{-8}$ *M*, and for analysis calibration curves have to be used. The use of anodic oxidation does not seem to be promising for direct determination of individual anthracyclines in physiological materials. Interferences could be expected from aromatic amines and hydroxic compounds present in such samples. However, such oxidations of anthracyclines appear to be well suited for determination of closely structurally related metabolites following their separation by liquid chromatography.

### *2. Cathodic and Anodic Processes*

#### *a. Simultaneous Assay of Two Active Agents (Phenylbutyzone and Oxyphenbutazone) in One Formulated Form*

The anti-inflammatory drug phenylbutazone and its main metabolite oxyphenbutazone (used as drugs called Butazolidin® and Tanderil®) are reduced in unbuffered ethanolic solution. As the reduction probably involves that of hydrogen ion dissociated from 4-carbon,[186] it is not surprising that the d.p.p. peaks of the two compounds differ by less than 40 mV (Figure 12), and a simultaneous determination is thus impossible. Pulse polarography can, nevertheless, be used for determination of individual pure compounds[186,186a] (as well as of cetophenylbutazone and sulfinpyrazone[186]) in tablets and dragees, even in presence of dyes and excipients. Oscillopolarographic,[187] a.c., and s.w.p.[188] response is probably due to adsorption phenomena and was used for following the stability of phenylbutazone solutions and for assaying of this compound in injections.[188]

Oxyphenbutazone can be determined in the presence of phenylbutazone following the conversion of the former into a nitroso derivative.[189] Phenylbutazone under conditions used does not undergo nitrosation. As little as 10 ppm of the active compound can be determined by d.p.p. in some pharmaceutical preparations and in pure powder (cf. Table 3 in Reference 189). Tablets, capsules, and suppository excipients did not interfere. Simple dissolution in ethanol was sufficient. Differential pulse polarographic results compared well with the British Pharmacopeia method.

Alternatively both these anti-inflammatory drugs can be determined[190] by LSV and d.p.v. based on electrochemical oxidation at the glassy carbon electrode in a buffer consisting of 0.1 *M* sodium acetate and 0.1 *M* acetic acid in 98% ethanol (Figure 13). The oxidation possibly involves the carbanion-enolate form.[191] The phenolic group also facilitates the electrochemical oxidation of oxyphenbutazone. Our own measurements[115] have shown that traces of Tanderil® from 0.15% up to a few percent can be determined in butazolidine by d.p.v. (Figure 14).

#### *b. Simultaneous Determination of Butazolidin® and Prednisone*

This example illustrates the use of the cathodic and anodic processes for the assay of two active agents in the same formulated form, Delta-Butazolidin® dragees. Prednisone is determined by reduction using d.p.p. at the DME (Figure 15A). Butazolidin®, which is not reducible in the 0.03 *M* tetramethylammoniumhydroxide in 95% methanol supporting electrolyte, is determined by anodic d.p.v. at a rotating glassy carbon electrode (Figure 15B).[115]

## B. Kinetic Currents

Two types of organic reactions can be studied polarographically: (1) slower reactions taking place in the bulk of the solution and (2) fast reactions occurring at the surface

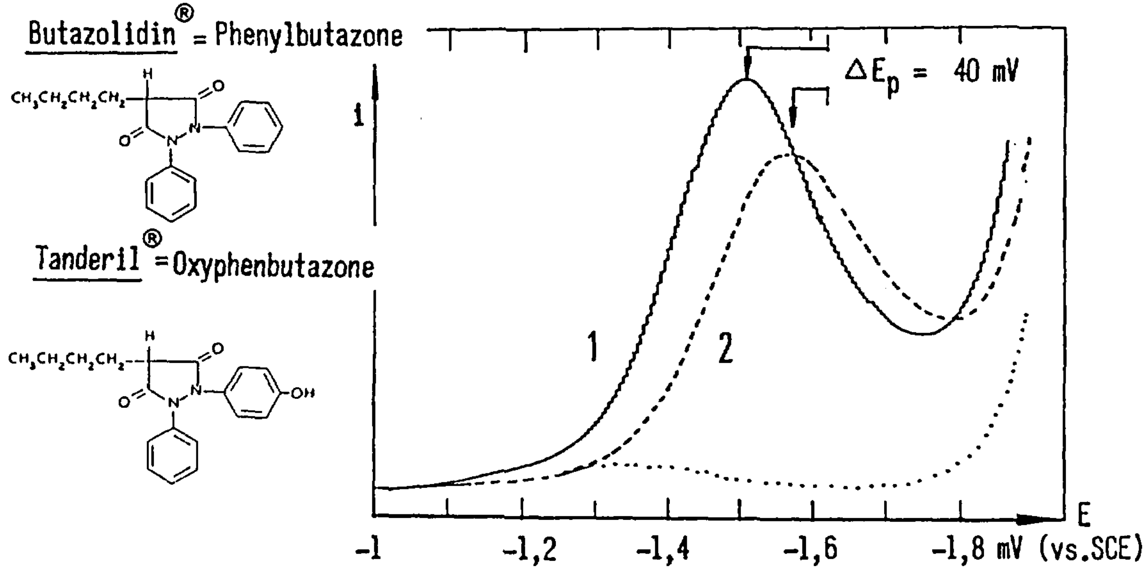

FIGURE 12. Differential pulse polarograms of phenylbutazone (1) and oxyphenbutazone (2) in 0.3 *M* lithium perchlorate in methanol with 2.5% water. d.p.p.: drop time 1 sec; scan rate 5 mV $sec^{-1}$; pulse amplitude −25 mV.[115]

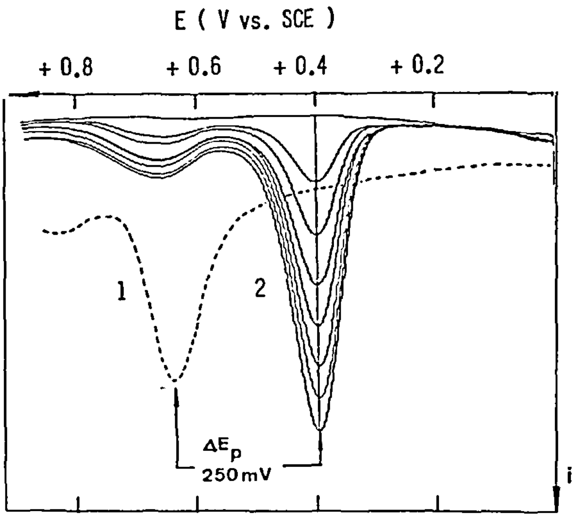

FIGURE 13. Anodic differential pulse voltammogram of phenylbutazone (1) and oxyphenbutazone (2) in 0.1 $M$ sodium acetate-acetic acid in ethanol with 2% water. Recorded at a stationary glassy carbon electrode. d.p.v.: scan rate 5 mV $sec^{-1}$; amplitude 50 mV.

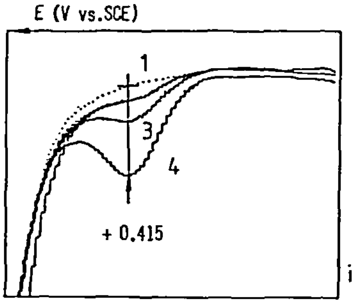

FIGURE 14. Differential pulse voltammetric determination of Tanderil® traces in Butazolidin® . (1) Blank in 0.1 $M$ sodium acetate-acetic acid in ethanol with 2% water. (2) 0.1%, (3) 0.16%, (4) 0.3% Tanderil® added. d.p.v.: scan rate 5 mV $sec^{-1}$; pulse amplitude 50 mV; sensitivity 20 μA full scale.[115]

of the electrode, where an equilibrium is disturbed by electrolysis and is reestablished rapidly. The theory of polarographic kinetic currents and their application in the study of reaction kinetics is dealt with in monographs[178,179,192] and reviews.[193,194]

Kinetic currents arise from a chemical process preceding an electron transfer that is slow enough to be the rate-determining step. In this section two examples of kinetic currents (waves) are given which can be used for the determination of organic compounds.

### *1. Aldoses and Ketoses*

Aldoses and ketoses give rise to kinetic currents. The wave height depends on the transformation rate of the nonreducible hemiacetal form to the aldehydo or keto form in the vicinity of the working electrode. The equilibrium concentration of the reducible form is negligibly small. For glucose, the fraction of the aldehydo form has been found

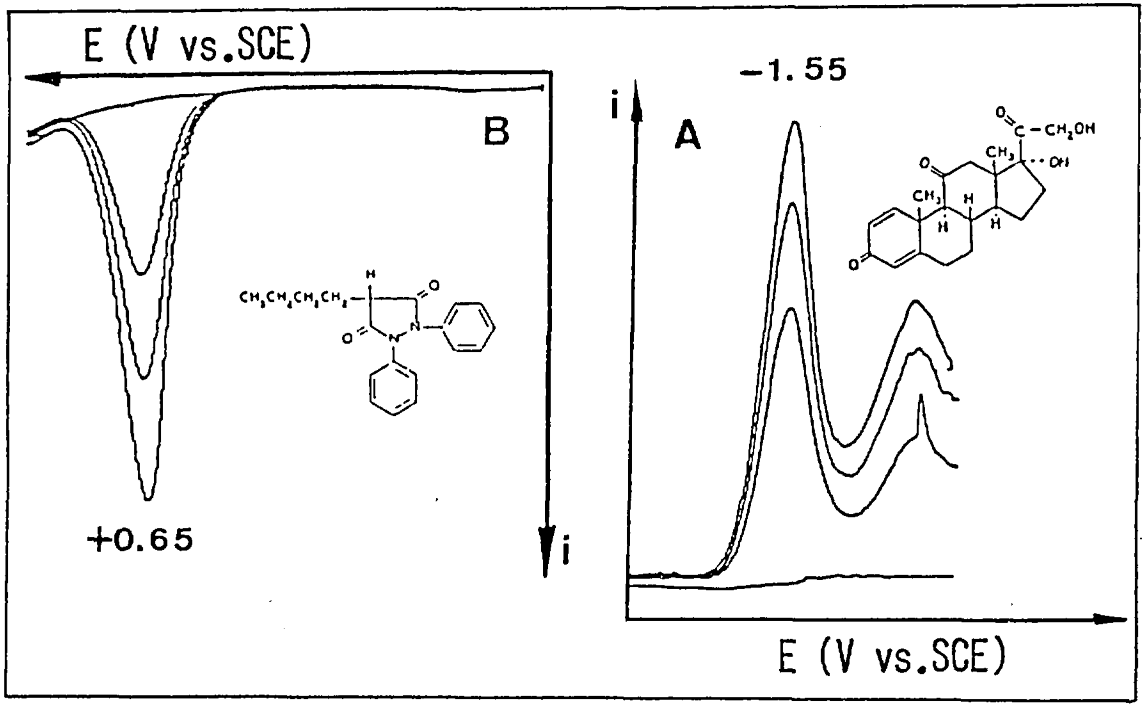

FIGURE 15. Direct determination of two active agents in one formulated dosage form (one single Delta-Butazolidin® drageé). (A) Differential pulse polarographic determination of prednisone in 0.027 *M* tetramethylammonium hydroxide in 95% methanol. (B) Anodic differential pulse voltammetric determination of Butazolidin® in 0.1 *M* sodium acetate-acetic acid in ethanol with 2% water.[115]

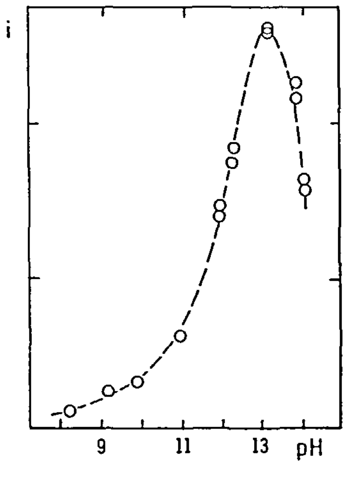

FIGURE 16. Reduction of formaldehyde at the DME. Current (i) as a function of the pH of the supporting electrolyte.

to be 0.003% of the analytical concentration of the glucose.[194] The concentration of the reducible form of aldoses is much less than for the ketoses.[196] Furthermore, the amount of the reducible form of hexose sugars is much smaller than for the configurationally corresponding pentoses, e.g., solutions of D-mannose at pH 7 contain 0.062% of the free aldehyde.

To determine fructose and mannose in mannitol, 0.0125 *M* $CaCl_2$ saturated with calciumhydroxide[197] was used. Using d.p.p., up to 10 ppm of fructose and 200 ppm of mannose can be determined in mannitol, often used as dilutent and excipient for solid and liquid pharmaceuticals.[115]

### *2. Formaldehyde*

Formaldehyde predominates in aqueous solutions in the hydrated form, $HCH(OH)_2$, but undergoes electroreduction only in the unhydrated form, HCHO. Polarographic reduction current is governed by the rate of dehydration, in which an electroinactive hydrated form is converted into reducible formaldehyde.[178,194,195,198-201] The rate of dehydration depends on pH and thus the limiting current also shows a strong dependence on pH (Figure 16). The steep shape of the dependence indicates that analytical applications of this wave must involve an accurate control of pH. Even at pH 13 the current is only about 20% of the diffusion current, which results in a somewhat smaller sensitivity. Because the rate of dehydration depends on temperature, the limiting current is sensitive to changes in temperature, much more than diffusion-controlled currents. Consequently, the temperature of solutions of formaldehyde subjected to polarographic analysis should be kept constant to at least 0.1°C.

Formaldehyde is currently used as a germicide, because of its bactericidal and bacteriostatic properties. d.p.p. can be used[115] to determine traces of formaldehyde in starches used as a dilutent in pills, tablets, and powders. Direct polarographic assay of suspensions in 0.1 *M* NaOH serves primarily to distinguish starches which have been treated with formaldehyde (with 800 to 900 ppm residual formaldehyde) from untreated starches. The lower detection limit of formaldehyde in such suspensions (presence of large amounts of undissolved material) was found to be of the order of 10 ppm using d.p.p. in untreated samples. For normal polarographic conditions as little as 1 ppm formaldehyde can be determined by d.p.p.[115,202] The polarographic determination of formaldehyde has several advantages over photometric methods such as reactions with chromotropic acid,[203] 2-hydrazinoisobenzothiazole,[204] 6-amino-1-naphthol-3-

Table 3
COMPARISON OF THE DIRECT DIFFERENTIAL POLAROGRAPHIC AND COLORIMETRIC (WITH CHROMOTROPIC ACID SUBSEQUENT TO A SEPARATION PROCEDURE) RESULTS OF FORMALDEHYDE ASSAYS OF TREATED STARCH SAMPLES

| Sample | Colorimetric assay (ppm) | Direct polarographic assay (ppm) |
|---|---|---|
| 1 | 810 | 858 |
| 2 | 910 | 947 |
| 3 | 325 | 348 |

sulfonic acid (J-acid), or 6-anilino-1-naphthol-3-sulfonic acid (phenyl J acid),[205] the drawbacks of which include storage instability of the reagents used and difficulties in purifying them.[206]

The polarographic method for the determination of formaldehyde in starch samples gives results 4 to 6% higher than the colorimetric method used[115] (Table 3).

Whereas the sensitivity of d.p.p. is comparable to that of photometric methods, that of d.c. polarography is significantly lower. Ignat'ev et al.[206] therefore suggested a d.c. polarographic method based on condensation of formaldehyde with 1,6-hexamethylenediamine in buffer solution at pH 10.4 to form a polarographically active Schiff base. A detection limit of 0.15 $\mu$g m$\ell^{-1}$, lower than those of spectrophotometric methods (0.5 to 1.0 $\mu$g m$\ell^{-1}$), was quoted.

## C. Catalytic Currents

Catalytic waves are currents observed in the presence of a substance (catalyst), often present in very low concentrations. A catalyst either causes a considerable increase in the height of a limiting current or occurrence of a reduction wave at more positive potentials than those at which reduction occurs in the absence of a catalyst. Various aspects of catalytic waves were dealt with in a monograph[192] and in review articles.[207-209]

Catalytic waves are sometimes observed for compounds which are neither reducible nor oxidizable. Because they are often one or more orders of magnitude higher than diffusion currents (e.g., for determination of cobalamin down to $10^{-8}$ $M$[79]), their use offers increased sensitivity. On the other hand, catalytic waves are usually a nonlinear function of concentration and their analytical application is possible over a relatively narrow range of concentrations using a carefully constructed calibration curve. Even more serious is their nonselectivity and their sensitivity to matrix effects, changes in pH and buffer composition, etc.[210] With the exception of waves in ammoniacal cobalt solutions, catalytic waves mostly cannot be used in the presence of proteins, other constituents of biological material, and polymers. Their use often is restricted to analysis of samples of simple composition containing only a single catalytically active species, as sometimes encountered in pharmaceutical analysis. Comparatively small reduction currents are sometimes given preference over the use of larger catalytic waves. An example of such choice is a study of pharmacologically active benzhydryl piperazine derivatives.[211]

Two main types of catalytic currents are encountered in determination of organic compounds: catalytic hydrogen waves in solutions of simple buffers and those in ammoniacal cobalt solutions.

### 1. Catalytic Waves in Buffers

In simple buffers some S-acids (such as thiols and proteins), N-acids (e.g., amines, heterocycles — in particular alkaloids), O-acids, and even C-acids yield catalytic waves corresponding to evolution of hydrogen at the electrode surface. The catalyst, which is regenerated in the process, is usually adsorbed at the electrode surface and decreases the hydrogen overvoltage. One of the possible mechanisms of this process is as follows:

$$\mathrm{Cat} \leftrightharpoons \mathrm{Cat_{ads}}$$

$$\mathrm{Cat_{ads}} + \mathrm{H^+} \leftrightharpoons \mathrm{CatH^+_{ads}}$$

$$\mathrm{CatH^+_{ads}} + e^- \rightarrow \mathrm{Cat_{ads}} + 1/2\,\mathrm{H_2}$$

where Cat is a symbol for the catalyst and subscript "ads" indicates adsorption at the electrode. The current in the presence of the catalyst flows at more positive potentials than in its absence, as the energy needed to reduce $\mathrm{CatH^+_{ads}}$ to produce $H_2$ is lower than that needed for reduction of $H^+$ on the same electrode (cf. also Reference 212). In some instances it is the reduced form of the compound which acts as the catalyst. Thus pyrithioxine (bonifen) is first reduced to 2-pyridox-3-thiol, which catalyzes the hydrogen evolution.[213]

The position of the acid-base equilibrium involving the catalyst depends on pH, and therefore catalytic waves of hydrogen evolution depend strongly on pH. Small changes in pH can result in large changes in the heights of catalytic waves. This acid-base equilibrium can also be affected by the presence of other acids, acting as cocatalyst. Components of the matrix can affect the adsorption of the catalyst. These factors contribute to the limited importance of catalytic waves in buffers in practical analysis.

Nevertheless, applications of catalytic hydrogen waves for analytical purposes appear even in the recent literature, and can be illustrated by the following three examples. The polarographic method was used for the determination of chloroimipramine (Anafranil® by Ciba-Geigy) in tablets.[214,215] In the pH range between 6.5 and 8 the catalytic wave is fairly well developed and permits quantitative determination with a standard deviation of less than 4% relative.[214]

The use of the hydrogen catalytic wave was suggested for determination of aprindin (3-*N*-diethylaminopropyl *N*-phenyl-2-indamin hydrochloride)[216] or in the photographic field for the assay of 4,6-dithiopyrimidino-1,3-3a-triazole used as stabilizer in photographic emulsions.[217]

### 2. Catalytic Waves in Cobalt Solutions

Compounds containing sulfhydryl or disulfide groups give catalytic waves in buffered ammoniacal solutions of cobalt (often called Brdicka catalytic waves) which have found applications, for instance, in structure analysis as well as trace analysis of proteins,[218] although the mechanism is not fully understood. It is assumed that zero-valent, Co(O), which is bound to one or possibly two SH groups to form a protein-Co(O) complex, may catalyze the hydrogen evolution before the complex is decomposed into Co(O) amalgam at the Hg[218,219] (cf. also references quoted therein). This catalytic wave in ammoniacal cobalt solutions is more suitable for use than the hydrogen catalytic wave in simple buffers as it is less prone to interferences than the latter. Two examples of recent applications in the pharmaceutical and medical fields demonstrate the practical use of Brdicka catalytic waves.

Using a catalytic wave in a solution containing 1.0 *M* cobalt (II), 0.05 *M* ammonia, 0.1 *M* ammoniumchloride, and 0.05 *M* tetrabutylammoniumhydroxide (Figure 17), it is possible to determine 0.5 to $5.5 \times 10^{-6}$ *M* (0.23 to 2.33 μg $m\ell^{-1}$) of pyrithioxine in

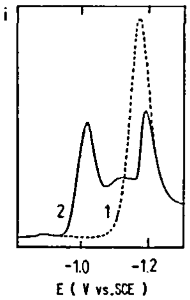

FIGURE 17. Differential pulse polarographic determination of pyrithioxine (in commercial tablet). (1) 0.1 $M$ NH$_4$Cl, 0.02 $M$ NH$_3$, 0.05 $M$ tetrabutylammonium hydroxide, 1 m$M$ Co(II), pH 9.1. (2) After addition of 1.7 μg pyrithioxine per milliliter of the polarographed solution.

pharmaceutical preparations, such as syrups, coated tablets, capsules, and suspensions.[213] Possible interferences from other electroactive substances present in samples are minimized by the high dilutions used, two orders of magnitude higher than those to be used, when utilizing the reduction cathodic wave. The method was verified[115] and found fast, sensitive, and satisfactorily accurate, as shown by replicate measurements.

Serum of patients suffering from cancer, after alkaline denaturation and removal of high molecular weight proteins by sulfoxalicylic acid, added to an ammoniacal cobalt (III) solution yields catalytic waves significantly higher than that of healthy individuals. In a recent modification for treatment of serum of patients suffering from urological cancers,[220] perchloric acid-soluble protein fractions (rather than sulfoxalicylic acid-soluble fractions) were used and measurements were carried out in the presence of a surfactant as maximum suppressor using d.p.p. Good correlations between the clinical classified stage of malignant growth and magnitude of the polarographic response were reported.

The most important limitation of the Brdicka reaction is the fact that the test is positive only at a more advanced stage of cancer. This prevents detection in early stages, when the patient can be more easily treated.[137] On the other hand, change in the height of catalytic waves proved to be an excellent diagnostical tool in deciding whether treatment or chemotherapy was successful.

In conclusion, the use of a comparatively small diffusion wave should be preferred to that of any of the catalytic waves for analytical purposes, whenever possible.

### D. Determination of Surface-Active Substances

The use of polarography in determination of surfactants is well established. Such analysis can be based either on surpression of maxima of first and second kind,[11,165,221,222] on occurrence of tensammetric waves in a.c., square wave, or pulse polarography or CV, or on effects on limiting currents and half-wave potentials of other electroactive species.

#### *1. Suppression of Polarographic Maxima*

The suppression of polarographic maxima (Figure 18) (which result from streaming of the solution in the vicinity of the electrode) caused by surface-active compounds permits the determination of low concentrations down to 0.1 to 1 mg $l^{-1}$ of surfactants. A serious drawback is the limited selectivity of these procedures. The method was extensively used for the evaluation of the purity of water, effluents, and other aqueous media; evaluation of purity of refined sugars;[222] and also in other fields as exemplified

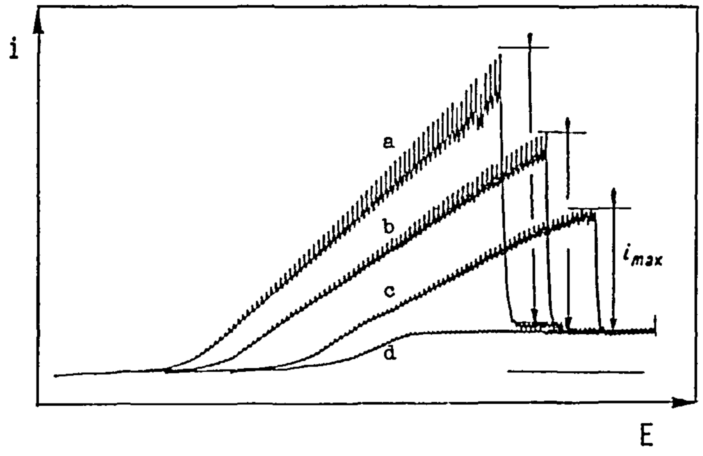

FIGURE 18. d.c. polarogram of oxygen in 0.001 *M* KCl (a) prior, (b) after addition of 0.3 m*l* waste water, (c) after addition of 0.5 m*l* waste water, and (d) after addition of 1.5 m*l* waste water. Polarographed solution = 20 m*l*. (Polarograms recorded with two-electrode Metrohm Polarecord E 261).

by the determination of novocain amide in solutions in ampoules based on suppression of the oxygen maximum.[223] In the absence of other surface-active substances, 0.2 to 4 ppm indole melanin — which is a biopolymer important for the functioning of living organisms for which no other analytical method has been developed — can be similarly determined.[224]

The recent interest in the measurement and characterization of surface-active organic compounds in natural waters resulted in renewed activity in the application of suppression of maxima.[225,226] The surfactant activity is expressed in terms of activity of an arbitrarily chosen surfactant, e.g., Triton® X-100, by means of a calibration graph (Figure 18). The procedure was applied to saline and brackish water as well as samples of surface microlayers. A good correlation between such results and dissolved carbon levels has been reported.[225]

Methods based on maximum suppression are simple, rapid, and nondestructive and are sensitive to water-soluble surfactants, such as proteins, polysaccharides, and glycoproteins. Attempts are being made to increase selectivity of such procedures, e.g., by using a variety of maxima occurring at various potentials.

### 2. Tensammetry Employing a.c., Square Wave, and Pulse Mode

An alternative possibility to estimate the concentration of surfactants in solutions (which are neither reduced nor oxidized in a given potential range) is based on electrochemical detection of nonfaradaic processes, resulting from adsorption-desorption equilibria, which yield characteristic capacity peaks when methods using cyclic variation of applied voltage are used. A well-known example is the peak observed in the presence of octylalcohol in 0.5 *M* $Na_2SO_4$ using LSV or CV.[227] The use of double-layer capacity measurements for evaluation of purity of solutions was first proposed by Barker.[228]

#### a. a.c. Polarography

One of the most rapidly expanding techniques in the analytical use of a.c. polarography is the use of so-called tensammetric waves.[48] When a surface-active compound is added to a supporting electrolyte, two sharp peaks occur on the current-voltage curve: the peak at positive potentials corresponds to the adsorption, the one at negative potentials to the desorption of the surfactant. These phenomena are dealt with in detail in specialized monographs[229,230] for both fundamental and second harmonic a.c. polarography. A detection limit of 0.02 mg $\ell^{-1}$ of polyethylene glycol (average molecular weight 1000) was reported for the second harmonic mode at a stationary mercury electrode.[231]

Modified Jehring procedure was applied[232] to determination of polyoxynated *n*-dodecyl alcohols with as little as two oxyethylene units at concentrations down to 3 ppm with an accuracy of ±2.5%. The analysis is carried out directly in the surfactant solution containing 0.5 *M* LiCl, without preliminary extraction or filtration. The concentrations of unknown solutions are determined by using a calibration curve which is prepared daily of known surfactant concentrations in the range of 2 to 20 ppm.

Another example of practical application of tensammetry is the stability control of thiamin hydrochloride (vitamin $B_1$) during the sterilization process.[233] For measurements of vitamin $B_1$ a linear dependence of peak current on concentration was found[115] for 25 to 100 mg $m\ell^{-1}$ 1 *M* KCl.

Tensammetric methods are in routine use in Kodak (Austral-Asia) processing laboratories for determination of color developing agents of the *p*-phenylenediamine type[234] and polyethylene glycols[235] in photographic processing solutions. In other recent applications tensammetric measurements of surfactant mixtures were studied.[236,237] These more strongly adsorbed surfactants can displace less strongly adsorbed surfactants from the electrode-solution interface.

Determination of traces of surfactants in distilled, potable, and untreated waters and in supporting electrolytes by tensammetry combined with accumulation on the HMDE at constant potentials in stirred solutions was described by Bednarkiewicz et al.[238] The total time of analysis does not exceed 15 min. The proposed method permits the efficacy of different purification procedures to be compared quantitatively.

### b. Square Wave Tensammetry

A particularly novel application of square-wave tensammetric response is the characterization of approximate average molecular weights of polymers.[93,94] This technique can also be used[239] for the determination of anionic, cationic, and nonionic surfactants and antistatic agents such as ethoxylated alkylphenols, alkylphosphates, and cation amine salts.

### c. Pulse Polarography

Differential pulse polarograms of surfactants also exhibit tensammetric (adsorption-desorption) peaks.[240] The dependence of the peak current on bulk concentration of a surfactant can be approximated as linear at lower concentrations but reaches a saturation limit at higher ones. Sensitivity can be increased by using a long drop time or a stationary mercury electrode coupled with an accumulation process. Levels of $10^{-7}$ *M* of polyethyleneglycol of nominal mean molecular weight 1540 (PEG 1540) were quoted. Modification of timing sequence of the PAR Polarographic Analyzer 174 permitted the determination of as little as $2 \times 10^{-8}$ *M* of this compound.[241]

### d. Evaluation of Tensammetric Methods for Determination of Surfactants

Tensammetric methods enable the determination of a large variety of low and high molecular surface-active compounds, many of which cannot be determined by other electrochemical, chemical, or other physical methods.[113] Their limitations reflect the limited possibility for analyzing mixtures of surfactants and possible matrix effects.

### e. Interferences of Tensammetric Waves

Tensammetric waves are useful for determination of surfactants, but can be a great nuisance in conventional polarographic work. Ethanol, for instance, produces a tensammetric peak on a.c. polarograms of methyltestosterone and progesterone in 50% ethanolic solutions with 0.5 *M* KCl or $KNO_3$ supporting electrolyte, which completely obscures the steroid wave.[242] Quarternary ammonium compounds were found to eliminate this tensammetric wave of ethanol so that tetrabutylammonium iodide was chosen as the supporting electrolyte.

Valuable to the practical analyst in the pharmaceutical field are the observations made by Jacobson.[243] The determination of drugs in tablets, creams, and ointments can be performed by d.p.p. without any previous separation, provided the drug is more strongly adsorbed at the electrode than the surfactant present in the formulation. Examples are chlorhexidin in Hibitane® antiseptic cream and thyroxine in Levoxin Mite tablets.[243] However, if the pharmaceutical formulation contains surfactants which are strongly adsorbed at the electrode surface, severe distortion of the polarographic wave may occur.[244] As capacity currents are not completely depressed when commerical pulse polarographic instruments are used, the polarograms exhibit tensammetric peaks, which often interfere in polarographic drug determination.[243,245] For example, 2-phenylindan-1,3-dione exhibits two well-defined waves at −0.95 and −1.26 V vs. SCE in citrate buffer[246] pH 4.9. If dodecylsulfate is present in the sample, a large tensammetric peak appears at about −1 V vs. SCE. This tensammetric peak overlaps both peaks of the compound and prevents carrying out the analysis.[243]

### 3. *Effects of Surfactants on Limiting Currents and Half-Wave and Peak Potentials*

Adsorbed films of surfactants on the electrode usually decrease the rate of electron transfer and this often leads to decrease in peak current, even to complete inhibition of the electrode reaction, and also to a shift of the peak (half-wave) potential to more negative values (Figure 19A, B). The use of ultrafiltration using a millipore filter with 0.5-μm pore size was proposed[40] for the separation of interfering excipients in low-dosage contraceptive tablets in which the polarographic response of the active compound (laevonorgestrel and norethisterone) was completely eliminated. Recoveries of 100 ± 1% were obtained by the recommended method.

In certain cases, on the other hand, the presence of a surfactant in the formulation can also be of advantage in pulse polarographic determination of drugs[243] and organic compounds[115] (Figure 20). Surfactants with the same charge as the species under study act as electrochemical masking agents, whereas peak currents may be enhanced by oppositively charged surfactants.[247] The peak of riboflavin, for instance, increases by about 100% on addition of 200 μg methocel $m\ell^{-1}$ to a solution of $10^{-5}$ *M* riboflavin in phosphate buffer; the peak position is hardly affected.[243]

A similar increase in the peak current has recently been reported in d.p.p. determination of benzylpenicillenic acid upon addition of Triton® X-100 to the supporting electrolyte.[248] A 2- to 14-fold increase of the peak current was reported, depending on the concentration of the benzylpenicillenic acid.

Thus, when drugs are analyzed for organic or inorganic components in the presence of surfactants, the standard addition method is strongly recommended. Calibration curves — if used at all — must be obtained in the presence of the same concentrations of all surfactants present in the sample of the pharmaceutical, preferably in the presence of a placebo or the same amount of ointments or creambase. The analyst should be well aware that procedures for determining a given drug in one formulation will often not be suitable for other formulations due to interference from other excipients.

It must be stressed that the use of tensammetric waves in analytical work calls for extreme care and common sense.

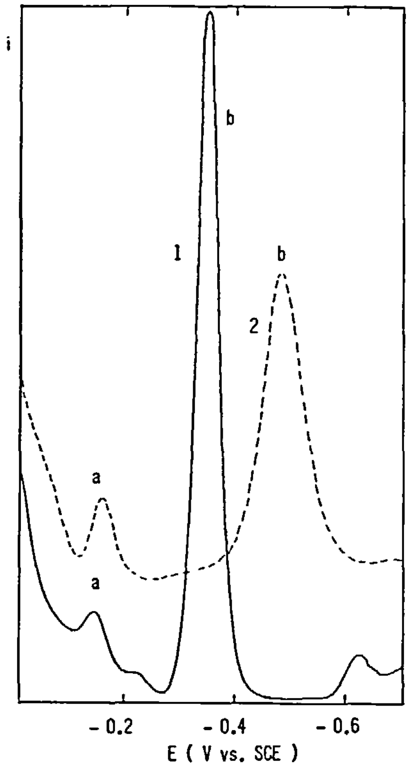

FIGURE 19A. Influence of Triton® -X-100 on height and position of the reduction waves of (a) 4,9-diaza-5,10-anthraquinone and (b) 4,7-phenanthroline-5,6-dione. (1) Prior, (2) after addition of 100 ppm Triton® -X-100.[115]

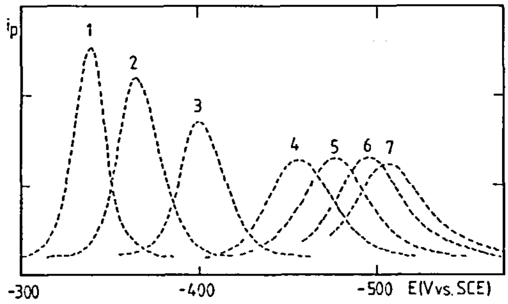

FIGURE 19B. Shift of the reduction peak of 4,7-phenanthroline-5,6-dione as a function of Triton® -X-100 added: (1) nil, (2) 25 ppm, (3) 50 ppm, (4) 75 ppm, (5) 100 ppm, (6) 150 ppm, and (7) 200 ppm.

## VII. PARAMETERS DETERMINING THE USEFULNESS OF POLAROGRAPHY AND VOLTAMMETRY FOR PRACTICAL ANALYSIS

Factors that determine the usefulness of polarography and voltammetry for the practical analyst are, among others, applicability, sensitivity, rapidity, selectivity, and specificity.[8,249]

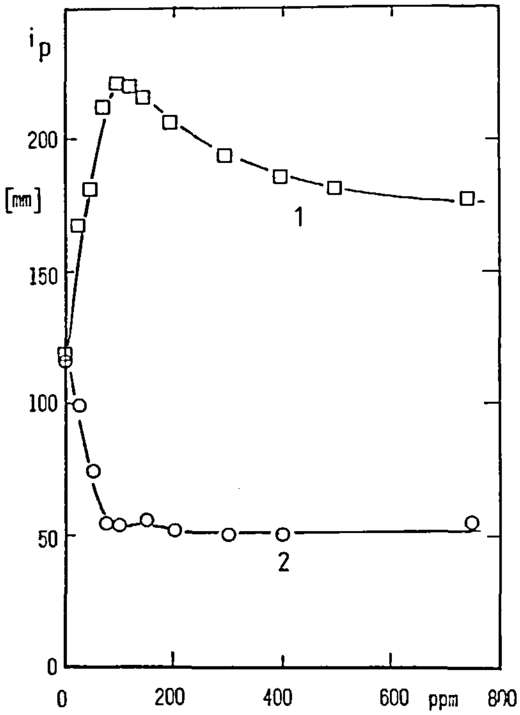

FIGURE 20. Influence of Triton® -X-100 on the differential pulse polarographic peak height of (1) 4,9-diaza-5,10-anthraquinone and of (2) 4,7-phenanthroline-5,6-dione.

## A. Applicability

The reproducibility of a polarographic and voltammetric determination is usually about 2 to 3% for the d.c. at the 20 to 0.01% level and for d.p.p. about 5% for samples containing 0.001 to 0.01%.* In general, polarography and voltammetry are thus more suitable for the determination of low concentrations of a given substance in a solution or mixture, rather than for quantitative assay (titer determination) of a pure substance. It can be recommended for titer determination if no method is available, if other methods are more tedious, more expensive, or less reliable or selective, or if it is essential to obtain an approximate result rapidly.[8]

## B. Sensitivity

### *1. The Sensitivity Provided by Different Instrumental Techniques*

d.c. polarography was the first instrumental method to allow quantitative determinations below $10^{-4}$ *M*. However, it was not until the advent of LSV, square-wave, and pulse polarography in the 1950s that the method was able to reliably determine submicrogram quantities. About two decades later a third generation of instruments (phase-sensitive a.c. polarography and d.p.p.) appeared, capable of even greater sensitivity. Modern polarography and voltammetry, under optimum conditions, have a sensitivity comparable to some gas-liquid and spectrofluorometric methods. The sensitivities of the individual instrumental methods currently used are shown[252] in Figure 21.

The d.p.p. detection limit of flurazepam and its major blood metabolites, for instance, was found to be 10 to 20 ng flurazepam per milliliter of plasma.[250] For constant

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* In the case of pharmaceutical assay, this is well within the limits specified by the British Pharmacopeia and adequate for body fluids.[249]

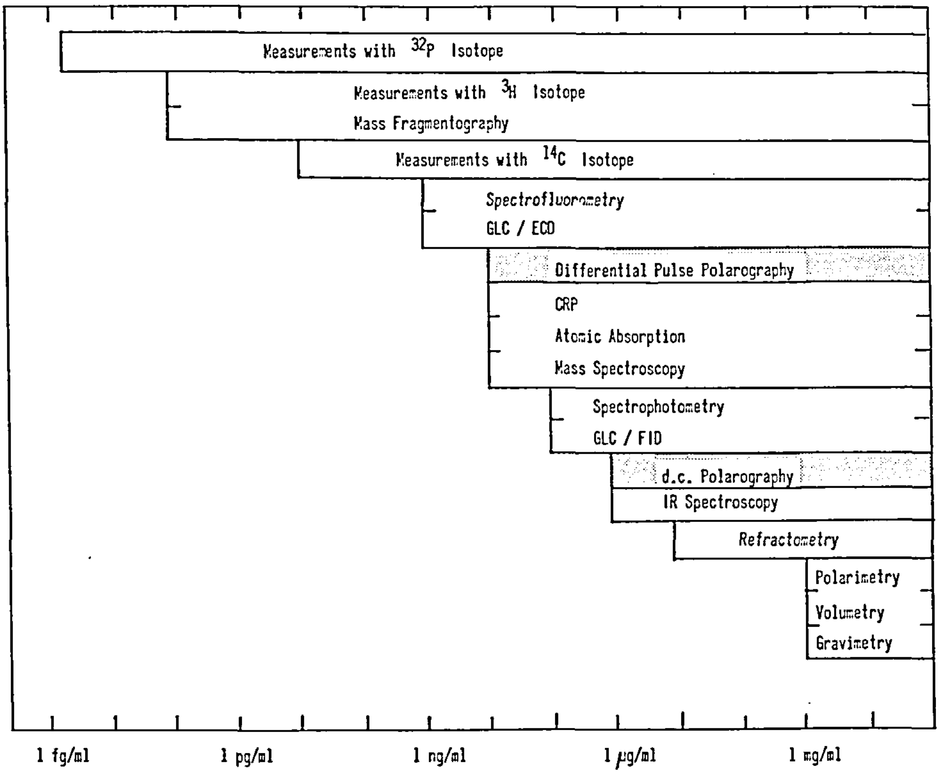

FIGURE 21. Sensitivities of polarography and related methods.[252]

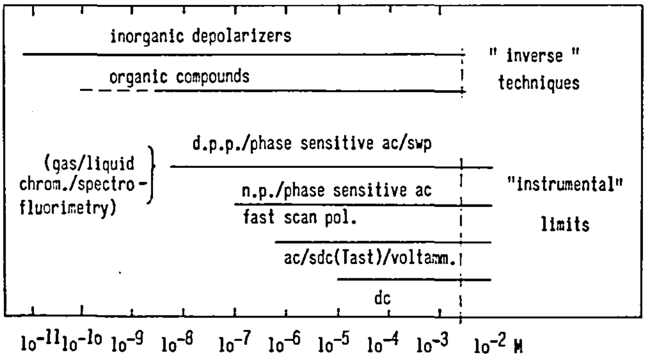

FIGURE 22A. Range of practical usefulness of polarographic and voltammetric techniques.[251]

potential pulse (c.p.p.) and alternative drop differential pulse polarography (a.d.p.) Vohra[74] gives a detection limit of $10^{-8}$ *M*. A distinction must be made between the sensitivity provided by the different available techniques (Figure 22A, "instrumental" limits) and increased sensitivity provided by stripping or "inverse" voltammetric techniques developed in the last few years[251] (cf. Tables 4 and 5). The limits of detection of the various electroanalytical techniques depends primarily on their ability to achieve a favorable faradaic-to-charging-current ratio. If the substance gives rise to a catalytic wave, the detection limit of d.c. is much lower: for cobalamin in buffered media it is about $10^{-8}$ *M*; for vanadium (V) in the presence of a large excess of $H_2O_2$ the detection limit may be as low as $10^{-9}$ *M*.[8]

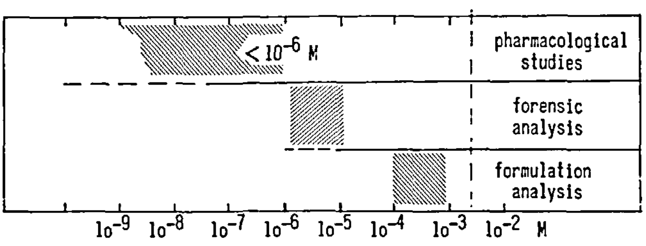

FIGURE 22B. Concentration ranges in drug analysis.[251]

Polarography is applicable over a much wider range of concentrations than most other instrumental techniques: zinc, for instance, can be determined from levels of less than 0.01 to 100 to 200 ppm in the same supporting electrolyte merely by adjusting the instrumental sensitivity. This is particularly useful when series of sampling points are being used and hence changes of two or three orders of magnitude are possible. A practical example is the determination of hydrazine in boiler water in a plant[115] by a procedure developed for LSV[253] and adapted to d.p.p. using as supporting electrolyte a 1:1 mixture of boiler-water-acetone in 0.05 *M* sulfuric acid. A linear relationship of the peak height of the hydrazone formed with acetone and the depolarizer concentration was observed[115] over the studied range of 10 to 2000 ppb.

Concentration ranges between $10^{-3}$ and $10^{-4}$ *M* (Figure 22B) encountered in analysis of formulations in pharmaceutical analysis are rather high compared with the sensitivity of modern polarographic instruments: for forensic analysis they lie between $10^{-5}$ and $10^{-6}$ *M*; for pharmacological investigations where concentrations are often lower than $10^{-6}$ *M*, the limits of the techniques are often reached, and separation and preconcentration are then necessary. In view of the large number of electrochemically reactive compounds, HPLC with electrometrical detection in particular has been widely adopted in drug metabolism studies. As the electrometric detection for HPLC is beyond the scope of this article, the reader is referred to the numerous recent publications in this field.[254-256]

### *2. Techniques to Increase the Sensitivity of Organic Analysis: Inverse Voltammetry of Organic Species (Cathodic Stripping)*

The search for more sensitive techniques than those available by instrumentation in organic electrochemistry led to the development of accumulation-stripping procedures. The extraordinary sensitivity of stripping voltammetry for organic compounds down to $10^{-9}$ to $10^{-10}$ *M*, cf. Table 4 (and even lower for inorganic systems as shown by Table 5), arises from preconcentration of traces of material onto a microelectrode followed by application of a voltage ramp which strips the substance from the electrode. The resulting current-voltage curve is recorded.

When the electrode is used as anode during the preconcentration period and as cathode in the stripping one, the technique is called "cathodic" stripping. Conversely, when the electrode acts as cathode during preconcentration and anode during stripping, it is called "anodic" stripping. For organic compounds the preconcentration can be achieved by:[258]

1. Preconcentration by adsorption of the species to be determined or of the product of an electrode reaction followed by cathodic or anodic stripping of the adsorbed species[259]
2. Andodic preconcentration as sparingly soluble salt or complexes with mercury ions followed by cathodic stripping

3. Complex or compound formation with excess of selected metal ion followed by determination of the remaining metal ion by anodic stripping voltammetry

The principles and conditions as well as the scope of application of stripping analysis have been dealt with in monographs[260,260a,261] and review articles.[262-264]

### *a. Preconcentration by Adsorption*

An example of this type is the determination of methylene blue at a HMDE[265] or on a wax-impregnated carbon electrode in the concentration range of $4 \times 10^{-5}$ to $4 \times 10^{-9} M$.[266] Traces of alizarin S can also be determined on a stationary mercury drop electrode.[267] The lower limit for a d.c. voltammogram was found to be $5 \times 10^{-9} M$.

A new electrochemical detection scheme for flow injection systems is based upon selective adsorptive accumulation either by spontaneous adsorption or by its covalent attachment to the surface via specific functionalization introduced to the surface of an analyte at the electrode surface followed by d.p.p. determination. Improvements in detection limits to about $10^{-9} M$ are quoted.[268] The main advantage is the high degree of selectivity toward adsorbed-attached electrode species. Reproducible assay of chloropromazine in urine with no sample treatment is possible in this way.[268]

### *b. Cathodic Stripping Voltammetry (CSV)**

CSV may be represented by

$$A^{n-} + Hg \underset{\text{stripping}}{\overset{\text{deposit}}{\rightleftarrows}} HgA + ne^-$$

In CSV the stripping current depends on the mercury compound formed at the surface of the electrode and is therefore independent of the electrode volume.[263] The stripping of the insoluble film from the mercury surface usually gives better peaks when compared with the anodic stripping used in inorganic analysis in which slow diffusion from the bulk of the mercury drop causes, for example, tailing.[270]

The most commonly used working electrode in CSV is the HMDE which is commercially available. An advantage of the HMDE is the availability of a clean electrode surface by forming a new mercury drop. The disadvantage is the presence of waste mercury in the cell, which may react chemically, e.g., with sulfur compounds and thus remove such compounds from the solution and cause low and erratic values.[263] For example, 200 $\mu l$ of elemental mercury stirred for 15 min with a $3.5 \times 10^{-7} M$ thioamide solution caused complete loss of the thioamide.[271] To avoid such interferences, Florence[263] used a small mercury pool electrode at the bottom of the cell. In this way all the mercury in the cell forms part of the working electrode. The disadvantage of this device is that the deposit was not removed by a single stripping scan. To clean the mercury pool, cathodic preelectrolysis was applied for 1 min at a potential sufficiently negative to decompose all the mercury compound. An alternative is to cover the waste mercury with a layer of carbontetrachloride, chloroform, or other liquid of high density, immiscible with water.[179] Extraction of the studied compound into this layer must be, nevertheless, considered.

### *c. Sulfur-Containing Coumponds*

Among the first sulfur-containing organic compounds studied by CSV were thiosem-

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* A chemical alternative to the conventional accumulation techniques entails the use of a chemically modified electrode. First a specific organic analyte is preconcentrated at the electrode surface via a selective chemical reaction, then the formed reaction product is determined (not stripped) quantitatively by conventional voltammetric techniques.[269] For ferrocene carboxaldehyde a detection limit of $10^{-7} M$ is quoted.

icarbazone,[272] thiourea, 2-mercaptobenzthiazole, 2,5-dimercapto-1,3,4-thiazole, thioanalide, rubeanic acid, and cysteine.[260] A rotating mercury-coated platinum electrode was found to be most suitable for cathodic stripping of sodium-diethyl-dithiocarbamate.[270] The authors assumed that it should be possible to lower the concentration limit to $10^{-9}$ and even to $10^{-10}$ *M*. Similar limits were claimed using differential pulse CSV (DPCSV) at an HMDE for the assay of the sodium salt of 2-mercaptopyridine-*N*-oxide.[273]

CSV has been employed successfully in different fields using different electroanalytical techniques, as shown by the following examples.

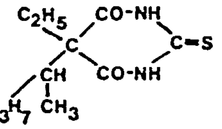
### i. Pharmaceutical Analysis

Thioamide drugs can be determined using CSV in plasma and urine down to $2 \times 10^{-8}$ *M*. CSV enables discrimination between primary and secondary thioamides, because the primary thioamides form electrolytically mercury salts at less positive potentials. CSV is, on the other hand, not feasible for the tertiary thioamides.[274] Naturally occurring sulfur compounds such as gluthathione, thiamine, methionine, cystein, cystin, and hydrogen sulfide and anionic species such as $Cl^-$ do not interfere. The detection limit of $2 \times 10^{-8}$ *M* is said to be achieved. The results in plasma are accurate, with a precision of 2.9% at a $5 \times 10^{-7}$ *M* level on 2-m$\ell$ samples.

The possibility of using CSV for the determination of sulfide ions ($HS^-$) and thiols in the presence of vitamin $B_{12a}$ at physiological pH was demonstrated.[275] A cathodic pulse that strips the adsorbed films of cystein and $B_{12a}$ produces a separate peak for each substance.

Cyclic voltammetric and pulse polarographic studies of 3-thiobarbiturates resulted in the development of CSV methods which are more sensitive (0.24 to 4.8 ppm) than methods involving d.p.p. (1.3 to 24.2 ppm).[276]

Compounds (I) and (II) produce at the anode mercury salts (Hg-S-R) at the surface of the electrode and are thus amenable to CSV analysis down to about $10^{-6}$ *M*. Compound (III) undergoes oxidation in which $S^{2-}$ is formed which is plated as HgS. The sensitivity of the CSV determination is also about $10^{-6}$*M*.



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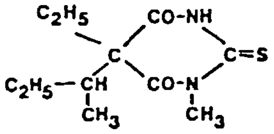
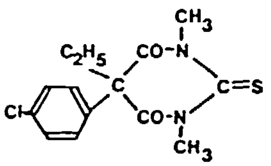
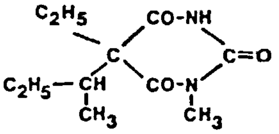


II



III

Compound (II) can be determined in the presence of its main metabolite (IV), the oxygenated analog phemitone. The metabolite (IV) also probably forms a complex with mercury, but at considerably more positive potentials than compound (II).[191]


IV

Chloride, which is a major source of interference in the direct analysis of biological fluids for such sulfur-containing organic molecules, does not interfere in the CSV methods.

#### ii. Analysis of Chemicals Used in Agriculture

CSV was applied to determine pesticides containing thiourea (V), phenylthiourea (VI), and $\alpha$-naphtholthiourea (VII).[277,278] Although DPCSV is potentially a more sensitive technique than linear potential sweep CSV (LPSCSV), in this case the sensitivity of the DPCSV is limited by the background interference. The stripping techniques both offer greater sensitivity than d.p.p., but the d.p.p. signals for (V), (VI), and (VII) can be distinguished whereas in CSV this is not possible. For the choice of operating technique: (1) the range of concentration likely to be encountered, (2) the constituents of the mixture, and (3) the time for analysis must be considered.[277] Because of its high sensitivity and short time analysis, LPSCSV has been used for direct determination of thiourea in urine. Such a method could prove useful in screening patients who have been exposed to foreign sulfur compounds in the environment.[277]

Linear sweep polarography on slowly dropping mercury drops (t = 7 to 12 sec), using appropriate conditions of accumulation, allows determination of microamounts of insecticides derived from dithiophosphoric acids and fungicides derived from dithiocarbamic acids.[279] Using the same technique, biologically active compounds, such as mucochloric acid (HOC(O)Cl C = C(Cl)CHO) or $\gamma$-isomer of hexachlorocyclohexane, were determined.[279]

#### iii. Interference Due to Oxygen

Thiols are very readily oxidized by air in alkaline solutions. Much of the work on thiols has been done in slightly alkaline solutions, although acetate buffers have been used successfully.[275,280-282] The removal of dissolved oxygen by purging with an inert gas is therefore an essential preliminary step in CSV of thiols.

Moore and Gaylor[281] compared DPCSV to phase-selective a.c. stripping voltammetry (PSCSV) for the determination of water-soluble, volatile mercaptans. DPCSV is inherently more sensitive than PSCSV for trace mercaptan determinations. Nevertheless, PSCSV is said to be the superior technique for mercaptan analysis performed in the presence of oxygen, because of its ability to discriminate against oxygen reduction.* As a result, PSCSV appears to be suitable for analysis of volatile mercaptans, when inert gas purging to remove the oxygen is not practicable. The sensitivity limit is said to be near 1 ppb for sodium mercaptoacetate.

### *d. Determination of N*-Heterocyclic Compounds

Cathodic stripping can be applied to the determination of heterocyclic compounds not containing sulfur which react with the mercury ions formed at the electrode.[283-286] Pyridine bases, commonly occurring in nucleic acids, can be assayed in this way. Most of the CSV determinations were carried out in conjunction with DPCSV. The estimated detection limits of uracil and cytosine, for instance, are at the HMDE of the order of $5 \times 10^{-8}$ *M*. A significant increase in sensitivity might be achieved by increasing

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* Alternatively, a higher pH can be used, where RSH forms nonvolatile $RS^-$ and the solution can be purged.

Table 4
LOWER DETECTION LIMITS OF ORGANIC COMPOUNDS BY INVERSE VOLTAMMETRY

| | | Ref. |
|---|---|---|
| Uracil, cytosine, thymine | $5 \times 10^{-9}\ M$ | 286 |
| Adenine | $2 \times 10^{-9}$ | 285 |
| Methylated adenine deriv. | $1 \times 10^{-9}$ | 285a |
| Mercapto-pyridine-N-oxide | $8 \times 10^{-10}$ | 273 |
| Thioamide drugs in plasma, urine | $2 \times 10^{-8}$ | 271 |
| Ethynyloestradiol | $5 \times 10^{-9}$ | 287 |
| Penicillins | $10^{-10}$ | 289 |
| Felypressin[*] in local anaesthetic formulation | $5 \times 10^{-9}$ | 289a |
| Codeine | $5 \times 10^{-8}$ | 285b |
| Papaverine, intercaine | $10^{-7}$ | |
| Atropine, cocaine | $10^{-6}$ | |
| Percaine | $10^{-8}$ | |
| Vitamin $K_1$ | 10 ng $ml^{-1}$ | 290 |
| Thiourea | 2.5 ng $l^{-1}$ | 278a |
| α-Naphthylthiourea | 80 ng $l^{-1}$ | |
| Diphenylthiourea | 50 ng $l^{-1}$ | |
| Pesticides containing urea | 1 ng $ml^{-1}$ | 278 |

[*] Felypressin = peptide containing eight amino acids including cystine.

the mercury surface, using mercury film electrodes. Values obtained by DPCSV and LPSCSV differed only slightly.

Nucleotides and nucleosides derived from pyrimidine bases are inactive and do not interfere with the determination of bases. The bases can be determined even in the presence of an excess of proteins and DNA.

Purine bases can also be determined by means of CSV with about the same sensitivity of about $10^{-8}$ *M*. The detection limit of adenine, for instance, is given as $2 \times 10^{-9}$ *M*. When conventional d.p.p. is used, the concentration range is substantially lower with $10^{-5}$ to $10^{-6}$ *M*.[284,285]

In the case of these heterocyclic compounds it is necessary[285,286] to pay special care to the deposition potential. The range of optimum deposition potentials is usually narrow and is located at rather positive potentials. The region of optimum potentials for sulfur-containing organic substances on the other hand is considerably wider;[258] the stripping peaks usually appear at more negative potentials, generally around −0.5 V vs. SCE. The inability of Florence[263] to obtain CSV peaks for compounds which do not contain sulfur was attributed[286] to a choice of too negative deposition potentials. CSV peaks were also observed[263] for some pterins and porphyrins.

### e. *Miscellaneous*

Besides the aforementioned *S*- and *N*-heterocyclic compounds, trace amounts of steroids,[287] antibiotics,[288,289] and vitamins[290] as well as flavines[263] and flavones[263] are assayed by CSV.

Table 4 lists some lower limits quoted. In comparison, inorganic anodic stripping limits are shown in Table 5.

## C. Speed of Analysis

### 1. *Comparison of Polarography with Conventional Techniques*

Due to the price of single analysis and to the need for larger number of samples, speed of analytical procedures has become a more important factor. Duration of an analytical procedure is a somewhat ambiguous problem, as already mentioned in Sec-

Table 5
TYPICAL DETERMINATION LIMITS FOR Cd(II) AND Hg(II) IN ANALYTE SOLUTIONS AFTER DIGESTION OR IN NATURAL WATER SAMPLES AT RSD ±20% AS DETERMINED BY NÜRNBERG[257]

| Polarography at DME | μg/*l* | mol/*l* |
|---|---|---|
| Linear scan d.c. | 1000 | $10^{-5}$ |
| Phase-sensitive a.c. | 20 | $10^{-7}$[a] |
| Differential pulse | 5 | $5.10^{-8}$ |
| Inverse voltammetry (stripping) | | |
| Conventional ASV/ HMDE | 0.1 | $10^{-9}$ |
| DPASV/HMDE | 0.01 | $10^{-10}$ |
| Conventional ASV/ MFE | 0.01 | $10^{-10}$ |
| DPASV/MFE | 0.001 | $10^{-11}$ |

*Note:* DME, dropping mercury electrode; ASV, anodic stripping voltammetry; HMDE, hanging mercury drop electrode; DPASV, differential pulse anodic stripping voltammetry; MFE, mercury film electrode.

[a] Only for reversible signals.

tions IV.A and IV.B. In the absence of pretreatment procedures (digestion, separation) as was the case for the polarographic and voltammetric examples mentioned in the introduction, complete analysis can be performed and a read-out obtained in 5 to 15 min. The deaeration of the polarographic sample solution is often the most time-consuming step.

The direct polarographic determination of flumethasone (synthetic corticosteroid, 6α, 9α-difluoro-16α-methylprednisolone), for instance, is simpler and just as precise as the time-consuming* tetrazolium blue method of the USP.[291]

Figure 23 shows the differential pulse (curve 1) and the sampled d.c. (SDC) polarograms (curve 2). For the quantitative determination the first SDC step is used.[251] The polarographic assay is performed within 10 to 15 min.

### 2. *Automation of Polarography and Voltammetry in the Organic Field — in the Analytical Laboratory and in Industrial Process Control, Quality Control, and Environmental Protection*

The increasing demands for large numbers of analyses in production and control, especially in the pharmaceutical field, in environmental studies, and also in pharmacological studies, have led to the development of various automated methods of analysis. The United States Pharmacopeia[292] and the British Pharmacopeia,[293] for instance, require in certain cases tests for content uniformity. At least ten individual dosage units (tablets, capsules, etc.) have to be analyzed. The introduction of content uniformity tests in the quality control laboratory has increased the work load by at least tenfold,

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* According to the USP procedure:[291] (1) to each of the flasks containing the standard preparation and the assay preparation, and to a similar flask containing 10.0 m*l* of alcohol to provide the blank, 1.0 m*l* of tetramethylammonium hydroxide TS is added, mixed, and allowed to stand accurately for 20 min; (2) after adding 1.0 m*l* of blue tetrazolium TS to each flask and standing further for 40 min, the absorbance can be measured following addition of 1.0 m*l* glacial acetic acid to each flask.

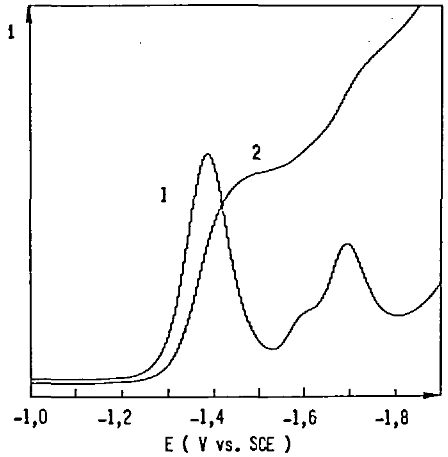

FIGURE 23. Differential pulse polarogram (1) and sampled d.c. polarogram (2) of flumethasone in 0.04 *M* tetraethylammonium hydroxide in 95% methanol. d.p.p.: drop time 1 sec; scan rate 5 mV $sec^{-1}$; pulse amplitude −10 mV.[251]

making automation of assays desirable.[294] Content uniformity control lends itself to automation as all samples are very similar in composition. Due to the smaller sample amount in the single dosage unit, it is not always possible to use the same methods as for the batch assay of homogenized units; for instance, d.p.p. is used instead of d.c. In connection with automation, a remark by Horwitz[295] is worth noting for the practical analyst. He states in his paper on "The Variability of AOAC Methods of Analysis as Used in the Analytical Pharmaceutical Chemistry": "The data with respect to automated methods are certainly more precise, if not accurate, than the manual methods. Even the within-laboratory precision is no better than that of the manual methods! Note, however, that there are far fewer outlines with automated methods than with other classes."

The automation of polarography and voltammetry has been dealt with in reviews.[139,296-299,310b,310c]

For automation the crucial problem is the automated deareation of the sample in flow systems before polarographic and voltammetric analysis. Different techniques were used: (1) addition of the oxygen-containing sample to an excess of deoxygenated streaming background solution;[300-302] (2) segmentation of the solution flowing through a mixing coil by nitrogen;[303] (3) bubbling argon through the sample cups just before aspiration;[304-304b] (4) deoxygenation of the solution by passing it through a gas-permeable silicon rubber tube surrounded by a second tube flushed with nitrogen;[305] and (5) an electrochemical scrubber containing porous silver to remove oxygen (metal traces and reducible organic impurities).[306] The nebulizer technique[64] was briefly discussed in Section IV.A. Another possibility would be to consider a.c. polarography, in which the presence of oxygen often does not interfere with recorded current-voltage curves. The lack of reliable automated commercial equipment for the rapid analysis of large numbers of samples has certainly delayed the widespread application of polarographic and voltammetric methods, for instance, in clinical chemistry.[307]

Methods for automated polarographic analysis of discrete samples in the analytical laboratory can be divided into: (1) nonmoving solutions (batch-type procedures) — sampling and storage of solutions for off-time determinations are often the source of many errors from chemical changes with time or in cases of determination of trace constituents from contamination, and (2) flowing solutions with continuous flow, segmented flow, and flow injection analysis.

The polarographic and spectrometric routine serial analyzer for content uniformity assays in pharmaceutical control built recently by Feher et al.[294] combines the advantages of flow and discrete analysis, the polarographic analysis of the sample solution (volume 2.5 m$\ell$) being carried out in a static solution. Advantages of the polarographic system are (1) it can be adopted to most modern polarographic techniques and various working electrodes can be incorporated into the polarographic cell, and (2) the possibility of simultaneous selective determination of components in mixture because a complete polarogram is usually run for each sample.

### a. *Batch-Type Procedures*

For the batch-type procedures a distiniction must be made between: (1) automation of the polarographic or voltammetric recording making use of automated controllers such as PAR Model 315A combined with the PAR 174A or the combination of Metrohm E 608-Polarecord 506 or 621 for unattended analysis, and (2) interfacing an automatic controller with an automatic cell sequencer to provide a totally automated voltammetric analyzer system, making unattended analysis of multiple samples feasible. The batch analyzer Model 136 for 36 samples combined with PAR 374 built at one time by Princeton Applied Research was on the market only for a short time and did not find wide acceptance. Characteristic for this type of analyzer is the high volume (from 2.5 up to 50 m$\ell$) analyzed.

### b. *Flowing Solutions*

For all streaming solutions either a slowly flowing side arm with a DME or usually an electrode with constant surface such as HMDE, Hg-pool,[309] mercury-coated[310-310b] electrodes or solid electrodes such as platinum, gold and carbon, carbon paste, wax-impregnated graphite, glassy carbon, and recently also reticulated vitrous carbon,[311] stationary and rotating,[312] are used. Different working electrodes and working principles (oxidation, reduction, cathodic stripping) in the operation of the cell in automated on-line analysis are summarized in Table 6 (see also References 310b and 310c). d.c. and modern pulse techniques, including square wave,[312a] are used in flow cells.

Constantly renewed electrode surface, extended potential range, and excellent reproducibility make DME-equipped polarographic flow cells well suited,[312a] although high flow rates cause problems because drop formation is influenced and may be not uniform.[310] The most serious disadvantage with solid electrodes is the nonrenewal of their surface,[310,313] the major problem being linked with maintaining a constant active surface area due to adsorption, film formation, etc. Cleaning of the electrodes and their maintenance are often difficult.

### c. *d.c. Mode*

The d.c. mode is very sensitive (see Table 6), exhibits a large linear calibration range, and has short response times and low noise levels.

### d. *Pulse Modes n.p.*

Pulse modes have higher noise levels. At correctly chosen initial potentials, adsorbed species can be stripped off or desorbed from the electrode surface. Fouling of the electrode is often effectively prevented and thereby long time stability is achieved, as the working potential is applied only for a short time, for most of the experimental time the electrode is at a potential where no electrochemical reactions occur.[310] In the normal pulse mode the current is nearly independent of the flow rate[310,314] and this mode should be used when a constant flow rate cannot be maintained. When the DME

## Table 6
## SUMMARY OF SOME SELECTED AUTOMATED ON-LINE ANALYSIS OF ORGANIC MOLECULES

| Method | Mode | Working electrode | Compounds studied | Concentration range studied | Sample rate (/hr) | RSD (%) | Ref. |
|---|---|---|---|---|---|---|---|
| On-line | d.c | DME | Nitroglycerine | 100 ppm | | | 318a |
| Seg. flow | d.c.<br>a.c. | RDME | Selected drugs in formulations | 0.4—10 mg/mℓ | 60 | 0.6—4.35 | 300, 301 |
| | d.c | RDME | ISDN in pharm. preparations | 0.5—5 mg/mℓ | 60 | | 302 |
| F.i.a. | d.c. | DME<br>HMDE | ISDN, dissolution experiments | 0.05—1 m*M* | 100 | | 302a |
| Cont. flow | d.c. | DME | Chlordiazepoxide diazepam | 10 mg/tablet<br>5 mg/tablet | 30<br>max. 48 | 0.6 | 304—304b |
| | d.p.p. | RMDE | Serum proteins | 5—50 mg/mℓ | 120 | 1 | 307 |
| | | | Seromucoids in human plasma | 1—30 mg/ℓ | 60 | 0.5 | 307a |
| | SDC<br>n.p.<br>d.p.p. | RMDE | Nitrobenzene | | | | 306a |
| Seg. flow | SDC | DME | Benzodiazepines | 5—25 ng/mℓ | 15 | 1.4 | 303 |
| Flow/ static | d.c. | DME | Formulated drugs | $0.3—50 \times 10^{-4} M$ | 30 | 0.7—1 | 176 |
| Cont. flow | d.c.<br>n.p. | Pt<br>C | *p*-Aminophenol<br>*p*-Nitrophenol | $4 \times 10^{-6}—5 \times 10^{-3}$ g/mℓ | 20 | | 308 |
| | d.c. | Silicon/C | Formulated drugs great variety of compounds dissolution rates | $10^{-6}—10^{-3} M$ | | | 307b |
| | d.c.<br>n.p. | Glassy C wall jet | *p*-Nitroso-*N*,*N*-diethyl aniline | $8 \times 10^{-5}—10^{-8} M$ | | 1 | 310, 310c |
| | d.c. | | Nitrazepam | $5 \times 10^{-4}—5 \times 10^{-7} M$ | | 3 | 310 |
| | d.c.<br>CSV | | 2-Thiobarbituric acid | $5 \times 10^{-5}—5 \times 10^{-6} M$<br>$5 \times 10^{-5}—5 \times 10^{-7} M$ | | 6—30<br>9—20 | |
| | d.c. | Glassy C wall jet | Chlordiazepoxide<br>Flurazepam<br>Oxazepam | $10^{-4}—10^{-7}$<br>$10^{-3}—10^{-7}$<br>$10^{-3}—10^{-6}$ | 60 | | 310c |

## Table 6 (continued)
## SUMMARY OF SOME SELECTED AUTOMATED ON-LINE ANALYSIS OF ORGANIC MOLECULES

| Method | Mode | Working electrode | Compounds studied | Concentration range studied | Sample rate (/hr) | RSD (%) | Ref. |
|---|---|---|---|---|---|---|---|
| | | | Lorazepam | $10^{-3}$—$10^{-6}$ | | | |
| | d.c. | Glassy C wall jet | 5,5′-Disubst. 2-thiobarbiturate | $1 \times 10^{-4}$—$1 \times 10^{-6}$ *M* | | | 310b |
| | CSV | MFE | | $5 \times 10^{-5}$—$5 \times 10^{-6}$ *M* | | | |
| | d.c. | MFE | 1,5,5′-Trisubst. 2-thiobarbiturate | $10^{-4}$—$5 \cdot 10^{-6}$ *M* | | | |
| | CSV | | | $10^{-5}$—$10^{-7}$ *M* | | | |
| | d.c. | MFE | 1,3,5,5′-Tetrasubst. -2-thiobarbiturate | $5 \times 10^{-5}$—$5 \times 10^{-6}$ *M* | | | |
| | CSV | | | $2 \times 10^{-5}$—$5 \times 10^{-7}$ *M* | | | |
| | d.c. | | Primary thioamide | $10^{-5}$—$5 \times 10^{-8}$ *M* | | | |
| | d.p.p. | Glassy C wall jet | Flurazepam, medazepam, chlordiazepoxide in formulations | 5—10 mg/50 mℓ methanol in routine tablet quality control | 30 | 2.5 | 316 |

*Note:* RDME, rapidly dropping mercury electrode; MFE, mercury film electrode.

is used, the current has been stated to be independent of the flow rate.[307] In the d.c. mode at the DME, after the flow rate has reached a certain level, the signal is found to be independent of the flow rate.[315]

Detectors which have been developed for HPLC can also be used in cases where chromatographic separation is not needed.

All these devices are characterized by low flow rates and small volumes. A cell with a small hold-up volume is essential for successful analyses of small sample volumes.[304a]

### e. *Automation of Industrial Processes*

For industrial process control, rapid continuous monitoring is essential if corrective action for variations has to be made rapidly.[317] Continuous enclosed sampling systems with fast flow rates interphased with a sensitive mircoprocessor-controlled analytical technique must be used.

Bond et al.[317] have recently developed a large capacity flow cell for maximum flow rates of 300 mℓ min$^{-1}$ enabling a response time of less than 15 sec. The SMDE employed allows interchange of polarography and stripping voltammetry. The cell design with respect to noise characteristics is associated with the maintenance of laminar flow.

Modern applications of industrial on-line polarography and voltammetry for continuous process control tasks, quality control, or control of effluents are scant and very little detailed information is to be found in the literature. Authors from Rhône-Poulenc[318] have given brief accounts of successful inorganic and organic applications over the last 10 to 12 years in industrial polarographic on-line analysis using slow DMEs in a by-pass. d.c. or pulse amperometry and differential pulse mode are applied.

## D. Selectivity* and Specificity

A serious shortcoming in qualitative analysis of electrochemical techniques in general is their poor selectivity when compared to separation-based techniques (chromatography). Compared with other direct methods (in particular spectrophotometry), electrochemical methods are often more selective. For reversible or quasireversible systems, the highest selectivity is achieved when those polarographic and voltammetric techniques are used which produce peak response, e.g., a.c., cathode ray LSV, d.p.p., and derivative methods (Figure 24).

For sharp and well-defined peaks, two peaks with potential values that differ by at least 40 mV can be resolved. In the presence of surfactants often at least 100 mV is necessary for distinguishing overlapping peaks. For species reduced at potentials several tenths of a volt more positive than the final rise of current corresponding to irreversible processes, d.c. polarography and normal polarography are often more selective than the a.c. and d.p.p.; the selectivity of LSV is the worst.

### *1. Limitations: Example — Determination of Nitroglycerine and Anticipated Decomposition Products*

The limitations of polarography due to poor selectivity are shown by the example of nitroglycerine. A d.c. polarographic assay method for glyceryl trinitrate using methylnitrate (BDH, Poole, U.K.) as internal standard gives results in good agreement with the BP method.[320] A d.p.p. method for glyceryl trinitrate single tablet assay was recently reported.[321] Minimization of sample preparation and of the effects of tablet excipients on the polarographic response was emphasized. Nitroglycerine on lactose substrate or in single sublingual capsules can be determined directly by d.p.p., but not always by conventional chromatographic methods in the case of nitroglycerine/lactose. The polarographic determination of nitroglycerine is thus simpler, faster, and just as

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* The reader should consult the paper by Inczédy[319] and the references therein.

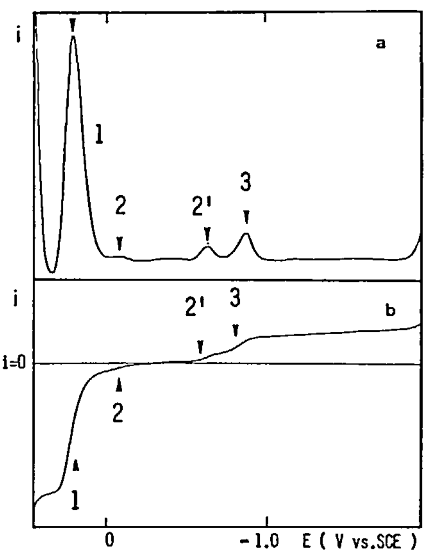

FIGURE 24. Differential pulse polarograms (a) and sampled d.c. polarogram (b) of dianthranol in 0.05 *M* tetraethylammonium perchlorate in methanol. (1) Dianthranol; (2,2') unidentified impurities; (3) bianthrone. Dianthranol concentration = 271 μg/m*l* polarographed solution. d.p.p.: drop time 1 sec; scan rate 5 mV $sec^{-1}$; pulse amplitude −25 mV; sensitivity 20 μA full scale.

precise as official methods. Recent reports, however, have indicated that intravenous nitroglycerine solutions lose potency when prepared or stored in certain containers.[322-328] This may be due to degradation or adsorption on a plastic matrix.[328] Thus a rapid and accurate assay of nitroglycerine intravenous solutions is needed. The breakdown of nitroglycerine occurs by a stepwise loss of nitrate groups,[322] as shown in Figure 25.

Accurately measured[251] peak potentials have the following values. Nitroglycerine: −990, −1020 mV; 1,2-dinitroglycerine: −965, −1090 mV; 1,3-dinitroglycerine: −1040 mV; 2-nitroglycerine: −1030 mV; 1-nitroglycerine: −995 mV vs. SCE using 0.01 *M* tetramethylammonium chloride with 0.01 *M* $NH_3$ and 0.01 *M* $NH_4Cl$ in 80% 2-propanol.[329] These figures show that the selectivity even of d.p.p. is not sufficient for simultaneous determination of the main and various degradation products of nitroglycerine, all of which, with the exception of glycerine, are polarographically active. As shown in Section VII.D.3, in some cases the selectivity of polarography can be superior to that of other techniques.

### *2. Advantages of Limited Selectivity: Use of Polarography When Selectivity Is Not an Indispensable Prerequisite*

In some cases a lack of selectivity can even be useful, e.g., when knowledge of the individual metabolites is not essential. Direct d.p.p. can be used[251] to determine the sum of the experimental nitro drug CGP-X and its biological nitro metabolites in the blood and urine of dogs, rats, and primates in large-scale resorption and toxicity studies. Reasonably good agreement between polarographic results and those based on $^{14}C$ studies was found (Figure 26).

A difference after 48 hr arises because polarography determines cathodically only the nitro moiety, while the $^{14}C$ technique corresponds to the whole molecule. This difference corresponds to nonnitro metabolites, mainly amines. These can be determined, if necessary, by anodic oxidation using voltammetry with carbon (paste) elec-

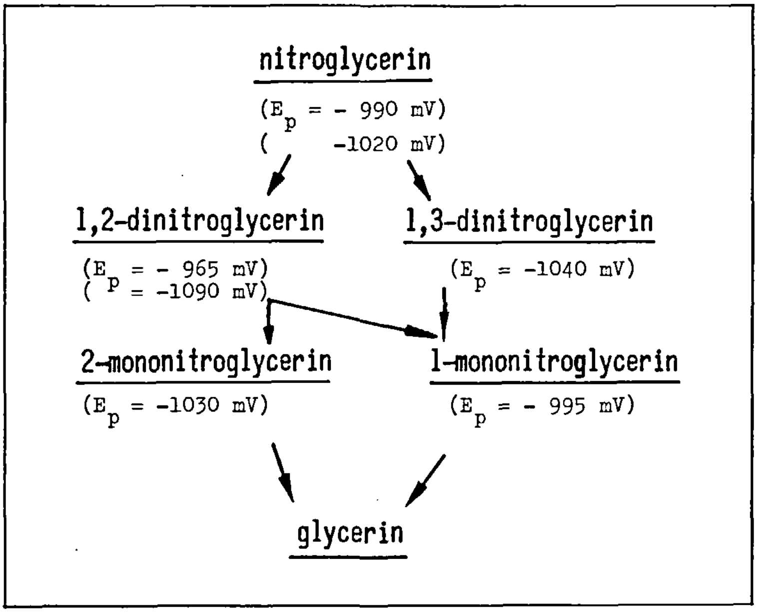

FIGURE 25. Degradation scheme of nitroglycerine and anticipated decomposition products.[322] In brackets are given d.p.p. peak potentials measured in 0.1 *M* tetramethylammonium chloride, 0.01 $NH_3$, 0.01 *M* $NH_4Cl$ in 80% 2-propanol.[329] (Peak potentials measured vs. SCE.)[251]

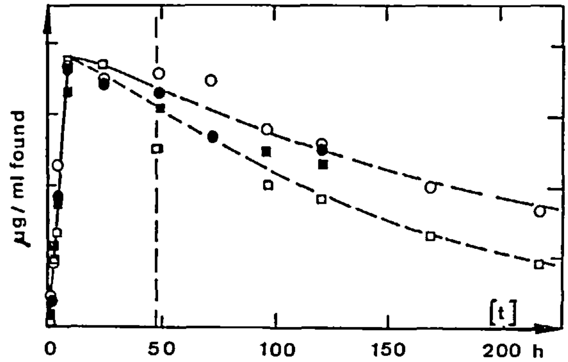

FIGURE 26. Resorption studies of $NO_2$-CGP-X. Differential pulse polarographic determination of total $NO_2$-CGP-X plus $NO_2$-metabolites in dog blood. ■ ● $^{14}C$ method; □ ○ d.p.p.: (○) 5 mg $kg^{-1}$, (□) 20 mg $kg^{-1}$.[251]

trodes. Hence polarography offers information about the fate of the total of nitro forms, whereas $^{14}C$ studies only about the fate of the sum of the nitro compounds and amino metabolites.

### *3. Use of Polarography and Voltammetry for the Identification of Organic Substances*

Overoptimistic presentations of modern polarographic instruments often claim that the selectivity and specificity characteristics of the instruments permit unequivocal identification even of complex substances and complex systems, even by an untrained user.

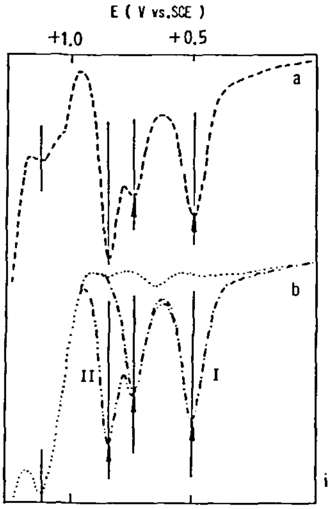

FIGURE 27. Anodic differential pulse voltammograms of sample (a) and sample-free matrix (b) after addition of stabilizer (I) and (II), recorded in a mixture of 0.12 *M* sulfuric acid and benzene and methanol at a stationary glassy carbon working electrode. Scan rate 5 mV $sec^{-1}$; pulse amplitude 25 mV.[115]

Polarography is useless for identification of molecular frame for which NMR and MS are methods of choice, but can be used for identification of functional groups in some special cases, when IR is not reliable (e.g., for some CO, $NO_2$ compounds) and in particular in proof of conjugation and its extent. As an example, identification of a nitro group on an aliphatic chain can be quoted. Nitroalkanes give a four-electron reduction wave accompanied by another wave which is caused by further two-electron transfer corresponding to the reduction of hydroxylamine formed at the electrode surface. The presence of two waves, the decrease of the more positive wave at pH 3 to 4, and the decrease of more positive wave at pH 10 (due to the carbanion formation) are so characteristic for the reduction of the aliphatic nitro group that the appearance of two such waves and their dependence on pH can be considered as proof of the presence of a nitro group bound to a saturated carbon.[195] Thus identification is possible in some cases, but only in very experienced hands.[191]

Polarography and voltammetry cannot be recommended for routine establishment of the identity of compounds as is done with IR, NMR, and MS in industrial control laboratories.

In some cases polarography proves to be very valuable as demonstrated by the assay of merthiolate [thiomersal = ethyl(sodium o-mercaptobenzoato)mercury (I)].[115] Merthiolate is currently used as a topical antiseptic and preservative in different pharmaceutical formations such as nasal and eye drops and is the preservative of choice for contact lens care solutions.[330,334] Thiomersal is subject to thermal[331] and photodegradation[332] and gets lost in aqueous solutions in contact with rubber[333,335d] and plastics.[334] Since some of the degradation products may have a higher toxicity potential than the original thiomersal,[330] accurate analytical techniques are essential.

The polarographic behavior of thiomersal and its practical applications have been described in several papers.[335-335f] The great advantage of polarographic methods — thiomersal is determined directly by sampled d.c. and d.p.p. in nasal and eye drop solution after proper dilution with water or buffer[115] — is its specificity for the intact molecule (also true for recently developed HPLC methods).[330,330a,332] All other techniques based either on total mercury (such as atomic absorption)[336-336c] or total organic mercury lack specificity and do not reflect accurately the amount of thiomersal present in the sample.[330]

Dusinsky and Faith[337,338] proposed oscillopolarography[339,340] (recording of $dE/dt = f(E)$ with constant current amplitude) for the rapid identification of medicaments and venoms, based on tabulated Q-values.[338]

An unequivocal identification will in most cases be possible only by standard additions of the pure substance. As an example, it is possible to quote the analysis of a resin sample for which the patent indicated the presence of 20 different compounds including undisclosed phenolic stablilzers. Recording of an anodic voltammogram before (Figure 27a) and after (Figure 27b) addition of two stabilizers (I and II) to a stabilizer-free matrix indicated the presence of two anodic peaks at +0.5 and +0.9 V for stabilizer (I) and one peak at +0.75 V (vs. SCE) for stabilizer (II). Similarity of position and shapes of peaks indicated presence of stabilizer (I) and (II) in the resin; peak heights correspond to concentrations in the 10 to 100-ppm range. The voltammetric results were corroborated by mechanical tests performed with resins made according to voltammetric findings.

Comparison with published data can in many cases provide useful information on the nature of the compound present, since even a larger molecule usually has only one or few electrochemically active functional groups. Published data can be found in tabular collections.[49,341-344]

As polarography is first and foremost a quantative method, polarographic and voltammetric identification should, when possible, always be supported by other, qualitative methods.

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