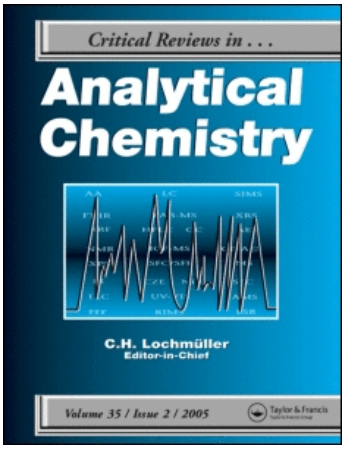

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APPLIED POLAROGRAPHY AND VOLTAMMETRY OF ORGANIC COMPOUNDS IN PRATICAL DAY-TO-DAY ANALYSIS PART II

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VIII. INTRODUCTION: EXAMPLES FROM THE ANALYSIS OF DYES, AGRICULTURAL PRODUCTS, PLASTICS AND PHARMACEUTICAL MATERIALS

In organic chemistry, polarography and voltammetry are most frequently applied for the solution of (1) practical, mainly analytical, problems. To show the scope and possibilities of these techniques in the analysis of dyes, agricultrual products, plastics, and pharmaceutical materials we shall briefly, and in a nonexhaustive way, discuss some practical examples. Polarography can also be used for (2) the solution of electrochemical problems, and (3) to provide useful information on fundamental problems of organic chemistry such as determination of equilibrium constants, and rate constants for fast ($t_{1/2}$ <0.5 sec) and slow ($T_{1/2}$ < 10 sec) reactions, detection of intermediates, etc. The reproducibility of polarographic measurements (about 3%) allows obtaining of kinetic data with a precision comparable to that of most other methods used in reactions kinetics. Because applications of the types (2) and (3) have been covered in sufficient detail elsewhere,[136,195,345,346] we shall restrict our discussion to type (1).

IX. GENERAL ASPECTS OF ANALYTICAL ORGANIC POLAROGRAPHY AND VOLTAMMETRY

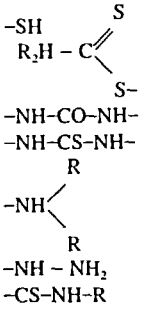
The analytical application of organic polarography and voltammetry can be divided into two large groups: 1° direct methods, 2° indirect methods.

Conditions for direct determination are that the electroactive substance to be determined is

1. Soluble in an appropriate protic or aprotic supporting electrolyte. Due to the great dilution used in organic polarography (10^{-3} - 10^{-8} *M*), many substances considered by organic polarography as completely insoluble are sufficiently soluble for the purpose of polarographic determination.[347] Nevertheless, solubility in stock solution and electrolyte mixture often represents one of the major problems in industrial analysis. When low solubility or stability, which is another serious problem, prevents use of aqueous solutions or of mixtures of water with miscible organic solvent, solutions containing an excess of an organic solvent with a small percentage of water or nonaqueous solvents are used[347] (see Section IX.C.).
2. Electroactive under conditions employed. The presence of reducible or oxidizable functional group (Table 7) is a prerequisite for the direct polarographic or voltammetric

Table 7
POLAROGRAPHICALLY AND VOLTAMMETRICALLY ACTIVE FUNCTIONAL GROUPS

Cathodic waves	Anodic waves
–Aldehydes, ketones	Amines
–NO	Phenoles
$-NO_2$	=P – O –
=C = C =	
=C = S	
=C = N–	Groups forming compounds with Hg and showing anodic waves
–N = N–	
–N = N – N =	
–O – O–	
–S – S–	
–C–Me	
–C≡N	
–NS	
$-SO, -SO_2$	
–SX	
–CX	
=P–R	



Note: –C–Me = metallic organic compound.

Table 8
REDUCIBLE FUNCTIONAL GROUPS CONTAINING N AND O ATOMS

$R–O–NO_2$	$+ 2e^-$	$\rightarrow RO^- + NO_2^-$
$R–NO_2$	$+ 4e^-, 4 H^+$	$\rightarrow RNHOH + H_2O + 2e^-, 2 H^+ – RNH_2 + H_2O$
$R_2N–NO_2$	$+ 6e^-, 6 H^+$	$\rightarrow RNNH_2 + 2 H_2O$
$2 R_2NH–NO$	$+ 4e^-, 3 H_2O$	$\rightarrow 2 R_2NH + N_2O + 4 OH^-$
R–NO	$+ 4e^-, 2 H^+$	$\rightarrow R–NH_2$
>NO·	$+ e^-, H^+ \rightarrow$	$\rightarrow$ >N–OH
$R_2N \rightarrow O$	$+ 4e^-, 4 H^+$	$\rightarrow RNHR + H_2O$
R–NHOH	$+ 2e^-, 2 H^+$	$\rightarrow RNH_2 + H_2O$
RC=NOH	$+ 2e^-, 2 H^+$	$\rightarrow RC=NH + 2e^-, 2 H^+ \rightarrow RCHNH_2$

determination. Substances lacking such a group may be determined by either indirect (see Section IX.B.) or by tensammetric methods.

A. Direct Methods

Numerous electroactive groups (some of them are given in Table 7) are involved in the polarographic and voltammetric analysis of dyes, plastics, agrochemicals, and pharmaceuticals.

A detailed discussion of mechanisms of these processes is beyond the scope of this article. The reader is referred to the literature on organic electrochemistry.[179,180,348–361] Some overall processes are summarized for nitrogen- and oxygen-containing compounds in Table 8. For example, electroactive pharmaceuticals often bear a keto or aldehydic group, an azomethine group (<C = N-), or a nitrogroup (e.g., chloramphenicol, nitrofurans), dyestuffs azo groups, azomethine, or carbonyl or quinoid systems and their nitrogen analogs, agrochemicals, sulfur, phosphorous, or halogen compunds, etc.

No simple rules can be given to predict whether or not an organic compound will be polarographically active in a given potential range, because the reactivity depends not only on the kind of the bond broken or formed during the electrode process, but also on the molecular skeleton involved and on the environment of the bond involved.[194]

Usually the majority of compounds bearing a given functional group behave in much the same way (e.g., nitrobenzenes, nitronaphthalenes, or nitrothiophenes, regardless of whether they are unsubstituted or bear such substituents as methyl, methoxyl, or carbonyl groups or halogen atoms), but some derivatives may differ, e. g., *o*- and *p*-nitroanilines, nitrophenols, and *p*-dinitrobenzenes show different reduction mechanisms.

B. Indirect Methods

Indirect methods are frequently used in polarography for the determination of organic compounds which are neither reduced nor oxidized in the available potential range or for which the polarographic waves are not suitable for analytical purposes, thus, making the technique available to a wide variety of compounds. Indirect methods have often been applied to pharmaceutical products[210] but also to pesticides,[362–365] plastics,[366–369] etc. A useful classification of these procedures is according to the origin of the wave which is measured.[347]

The wave arises from an electroactive substance which is prepared by a chemical reaction from the electroinactive substance to be determined. Chemical reactions used are derivatizations (nitration, nitrosation), condensations (formation of aldimines, ketimines, semicarbazones, hydrazones, oximes); additions (of bromine, etc.); substitutions (only rarely applied[179]); oxidations which can be chemical or electrochemical processes, followed by a subsequent reduction of the oxidation product, and hydrolysis.

The following examples illustrate the practical use of such procedures. For the determination of the polarographically inactive morphine and its derivatives, an indirect method has been proposed, based on treatment with nitrous acid[370] which results[371] in formation of 2-nitromorphine rather than a nitroso derivative. Alternatively, morphine can be determined after conversion into an N-oxide.[372]

The 2,4-D-type herbicide (see Section XII.A.1.b) is nonreducible and is determined after nitration of the extracted residue.[363] Among other pesticides which can be also determined by indirect polarography[373] are Malathion (after hydrolysis); Phorat (after hydrolysis); Dichlorvos (following hydrolysis and condensation); Carbaryl (based on nitrosation); DDT (using nitration); Folpet (based on reaction with cysteine); Warfarin (following reaction with iodine in alkaline medium); and Dalopon (after dehalogenation).

For the assay of promazine derivatives a number of indirect procedures can be used (Figure 28). In practical analysis a method is sought which is the most advantageous for the given problem.

Alternatively, it is feasible to measure the height of a wave of an electroactive reagent which reacts with the electroinactive substance. The reaction involved can be a condensation, addition, oxidation, or complex formation (some examples are given in Section XIII.A.).

Finally, some determinations based on catalytic (Section VI.C) and tensammetric waves (Section VI.D.2) as well as on amperometric titrations[179,374] can be classified as indirect methods.

C. Nonaqueous Medium

To increase the solubility of the compounds studied, to change the potential range, or to find conditions for recording of simpler, better-developed waves, nonaqueous solvents are used in organic electrochemistry with increasing frequency.[378–382] The use of such solvents often involves the use of special supporting electrolytes and reference electrodes. Methods for purification of such solvents, in particular enabling removal of traces of water, are of importance. It should be stressed that characteristic potentials ($E_{1/2}$, E_p, etc.) measured in various solvents are usually not directly comparable due to the uncertainty involving the

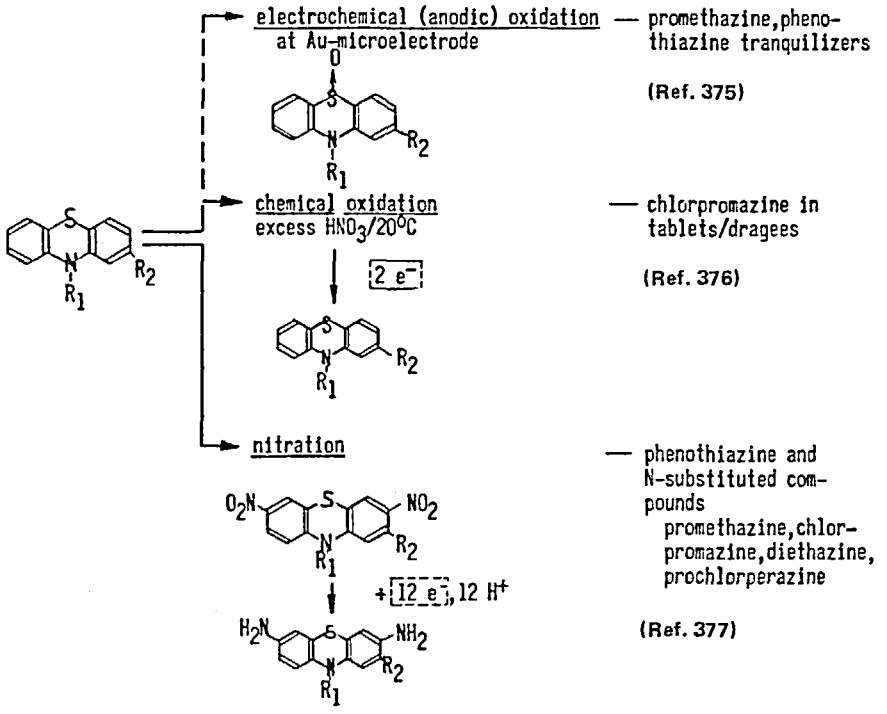


FIGURE 28. Indirect determination of promazines.

value of the liquid junction potential. Use of potential of a reference system (such as ferrocene-ferricinium ion,[383,384] colbaltocene,[383] Fe(*o*-phenanthroline)complex,[385] or *bis*-biphenylchromium[384] as a secondary standard is strongly recommended.[381] The difference between half-wave potentials of ferrocene and *bis*-biphenylchromium (I) is practically independent (1.12 to 1.13 V) of the solvent used. The chromium complex offers the additional advantage of being able to be used in mixed solvents containing water[384] and so, by extrapolation, potentials in water can be compared with potentials in nonaqueous solvents.[381,382] The number of generally applied practical analytical methods using nonaqueous solvents is still rather limited and such applications have a potential for growth.

The most widely used organic solvents employed are (1) nitriles (acetonitrile, benzonitrile); (2) amides (dimethylformamide, diemthylacetamide); (3) amines (methylenediamine); (4) ethers (tetrahydrofuran, dioxane); (5) acids (acetic acid); (6) alcohols (methanol, ethanol, 2-propanol); (7) sulfur compounds (dimethylsulfoxide, sulfolane); and (8) miscellaneous (propylene carbonate, nitromethane, methylenechloride, acetone). Inorganic solvents include, e.g., liquid ammonia and sulfuric acid (90 to 96%) which is currently extensively used[115] as solvent and supporting electrolyte for assays of various drug and dye intermediates.

Most solvents are used at 20 to 25°C, but there are exceptions. Benzonitrile, for instance, proved[115] to be useful for measurements up to 140°C. Some nonaqueous solvents offer the possibility of use over a wide range of temperatures, e.g., diallylcyanamide can be used[380] from −70 to +220°C. One of the properties which changes with temperature is viscosity (η), which affects the diffusion coefficient. For diffusion currents ($i_d\eta^{1/2}$) remains constant for the majority of systems studied, indicating increase in wave height (and hence, of sensitivity) with decreasing viscosity of the medium. Nevertheless, because of specific solvent-solute interactions, the validity of this relationship is not general.

The solvent often affects the "electroactivity range" which corresponds to the range of potentials in which a polarographic or voltammetric wave can be observed. In addition to

the nature of the solvent used, presence of residual water, and redox properties of cations and anions of the supporting electrolyte, this range also depends on redox properties of the solvent.[380] For example, the solvent radical anion formation of nitrobenzene plays an important role in limiting the range of negative potentials at a bright Pt electrode in the case of nitrobenzene containing 0.1 *M* quarternary ammonium solution.[380]

Cations of the supporting electrolyte mostly govern the limit at negative potentials provided that the medium is not too acidic. The ranges available with lithium and tetraalkylammonium cations depend on the solvent used. Whereas in hydroxylic solvents using mercury electrodes, tetraalkylammonium ions allow reaching of more negative potentials than lithium ions, in acetonitrile, nitromethane, and dimethylsulfoxide using platinum electrodes the situation is just opposite, the lithium ions enabling to reach more negative potentials. Anions of the supporting electrolyte determine the limit at positive potentials. In acetonitrile, ClO_4^- enables reaching of +2.5 V, whereas BF_4^- and PF_6^- of about +3.0 V (vs. Ag/0.2 *M* Ag^+ in acetonitrile).[380]

The nature of the electrode also defines the range, according to whether the electrode is an easily oxidizable metal, or a metal considered as inert.

The advantages of aprotic over aqueous media are (1) enhanced solubilities, also of the substrate, and minimization of adsorption problems; (2) usually wider useful available potential ranges when tetraalkylammonium salts are used: (3) reversible one-electron reductions can often be expected since organics with conjugated π-electron systems may be reduced to stable anion radicals; and (4) the sensitivity of a.c. and pulse modes may be higher than in water because there is a better chance of the electrochemical reversibility.[113,130] Use of such solvents can prevent undesirable reactions in presence of water (such as hydrolysis, hydration of inorganic species).[8,120,121] Nevertheless, as 0.01% w/v water corresponds to a concentration of 5×10^{-4} *M*, water can thus be in certain cases present in much larger concentration than that of the electroactive substance, so that undesirable processes may still be both fairly fast and fairly complete.[8]

However, these advantages may be counterbalanced by: (1) complexities caused by reactions of radicals or radical ions formed in these nonaqueous media or in the presence of unexpected proton donors, including the electroactive species;[8] (2) an increase in the iR drop due to limited ionization of electrolytes, which are often only slightly soluble. Tetraalkylammonium salts ($Cl;^-$, Br^-, I^-, ClO_4^-, PF_6^- BF_4^-) and lithium salts are generally used because of their better solubility in organic solvents. Tetraalkylammonium salts can, however, often exhibit specific adsorption effects. Several strong acids and bases are soluble in aprotic solvents, permitting the extreme points of the acidity scale to be reached;[347] and (3) difficulties involved in definition of acidity in nonequeous solvents, or with reference electrodes, liquid junction potentials, etc.[380-381]

1. Electrochemistry in Organic Solvents without Supporting Electrolyte

A requirement for a voltammetric solvent is that it is capable of dissolving salts of supporting electrolytes, a property not shown by hexane, for instance. This requirement limits the usefulness of voltammetric studies in numerous important areas of thermodynamics, kinetics, and analytical investigations. For example:

1. Reactions with solvents and/or supporting electrolyte salts preclude studies of a wide range of coordinately unsaturated compounds.
2. Measurements in high resistance solvents or at low temperature (the difficulty being normally the very high resistance in conjunction with the unsolubility of electrolytes) have not been possible.
3. Electrometric detection has been normally excluded in combination with normal phase chromatography which employs nonpolar organic solvents because of high resistance of such systems.[386]

4. The use of electrochemical probes has not been utilized for monitoring organic reactions carried out in nonpolar media.[386]

Recent work by Bond et al.[386] (for a theoretical treatment, cf. Reference 386a) demonstrates that platinum microelectrodes of radius smaller than 1 μm enable measurements of uncharged organic, inorganic, and organometallic compounds in different organic solvents like acetonitrile, dichlormethane, benzene, and acetone without or in presence of very low concentrations of added electrolytes. Oxidation of ferrocene in acetone can be followed down to −95°C when using such microelectrodes. HPLC-electrometrical detection using dichlormethane as chromatographic solvent was performed by incorporating a platinum microelectrode into a flow-through cell.[386]

D. Important Factors in Quantitative Polarography and Voltammetry

The reliability of the final results depends on the nature of the exploited signal (well- or ill-formed waves), the accuracy of the method, and on the other hand, on the calibration employed.

For analytical purposes, the most important rule is to measure all the curves to be compared in the same way, as precisely as possible.[387] Correction of the residual (blank or condenser) current is essential.[8]

The assumption that the residual current is unaffected by the substance to be determined seems justifiable for inorganic substances — there are exceptions — but this is less frequently so for organic substances. Organic substances and their reduction and oxidation products are often strongly adsorbed onto the electrode surface and thus affect the capacity of the double layer, and consequently alter the residual current. In the author's opinion, it is better to correct for the residual current by extrapolating the portion of the recorded curve that precedes the wave of interest, than to rely on a separately recorded residual current curve. Exceptions form waves close to final rise of current, particularly anodic waves of mercury salt formations.

1. Calibration Procedures

There are two kinds of evaluation of the concentration from recorded curves: (1) use of calibration curves, previously obtained with a number of known solutions covering the range of concentration of interest, and (2) simultaneous calibration and analysis by standard addition or pilot ion as internal standard. The pilot-ion method is rarely used in practice.

In practical analysis, the use of calibration curves is fraught with danger in view of matrix problems, especially in the study of formulations in the pharmaceutical and agricultural field, of biological samples, or production raw products. Therefore, when any organic compound or inorganic component is determined in biological or complex sample, the standard addition method is strongly recommended for determinations. In the author's laboratory, all determinations are made via at least three standard additions. Enough replicate measurements should be obtained to provide reasonably reliable estimates of the standard errors. A control of the constancy of the i/c is essential.

X. DYE INTERMEDIATES AND DYES

Practical applications of polarography and voltammetry will be demonstrated in this chapter on examples of some dye intermediates and dyestuffs.

A. Dye Intermediates

1. Voltammetric Determination of Sulfonation Products of Technical Samples in 96% Sulfuric Acid

The direct simultaneous determination of the different 2-oxy-naphtholsulfonic acids in

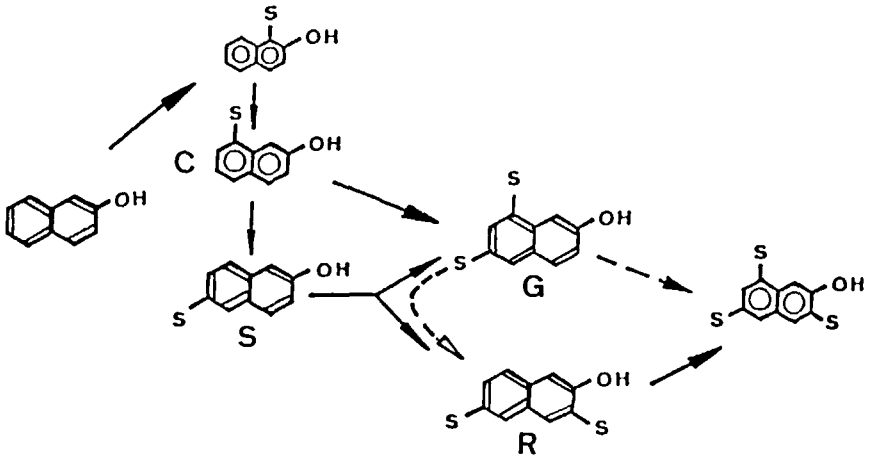


FIGURE 29. Direct sulfonation of 2-naphthol in 95% sulfuric acid. –S = sulfonic group; S = 2-naphthol-6-sulfonic acid; G = 2-naphthol-6,8-disulfonic acid; R = 2-naphthol-3,6-disulfonic acid.

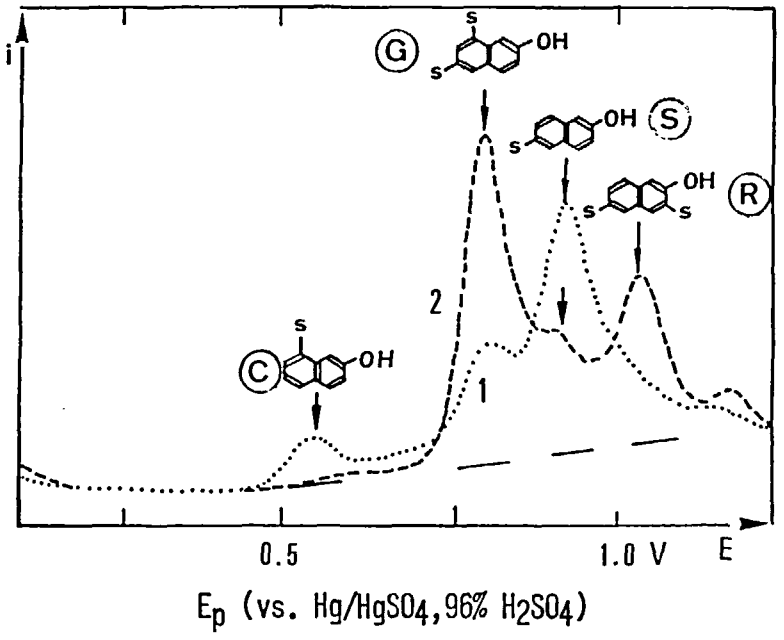


FIGURE 30. Anodic differential pulse voltammograms of a sulfonation reaction mass in 96.5% sulfuric acid, recorded at the beginning (1) (.....) after 5 hr at 40°C and at the end of the sulfonation (2) (- - -) after 15 hr at 80°C. Working electrode = platinum disc electrode. C = 2-naphthol-8-sulfonic acid; G = 2-naphthol-6,8-disulfonic acid; S = 2-naphthol-6-sulfonic acid; R = 2-naphthol-3,6-disulfonic acid.[115]

sulfonation reaction masses (Figure 29) is feasible using stationary platinum electrodes in about 96% (w.w) sulfuric acid which acts both as the sulfonation media and the supporting electrolyte.

Voltammograms at the beginning (1) and at the end of the sulfonation process (2)(Figure 30)[115] indicate the possibility of distinguishing individual naphtholsulfonic acids and following the progress of sulfonation. The results of the direct voltammetric method are in good agreement with the theoretical values and UV data; thin-layer chromatographic values tend

Table 9
COMPARISON OF THE RESULTS OF DIFFERENT METHODS FOR THE DETERMINATION OF G-, R-, AND S-ACIDS IN SULFONATION REACTION MASSES

Sample	Components	Theoret.	Voltammetry	TLC	UV
I	G	30.6	30.0	36.9	31.2
	R	31.8	32.1	36.3	27.7
	S	17.0	11.9	17.7	18.5
	mM/g_{tot}	2.81	2.57	3.20	2.76
II	G	45.8	45.1	49.1	45.6
	R	23.9	24.1	26.8	20.9
	S	8.5	8.0	9.3	9.3
	mM/g_{tot}	2.67	2.54	2.91	2.6
III	G	61.0	61.8	68.5	58.0
	R	11.9	11.9	15.2	12.6
	S	4.2	3.4	4.6	5.9
	mM/g_{tot}	2.59	2.57	2.94	2.58

to be too high (Table 9).[115] Some naphthol sulfonic acids give good auodic waves of the dropping mercury electrode due to Hg compound formation.[191]

2. Electroanalysis of Benzanthrone and Anthrone

Hydrodynamic voltammetry and polarography were employed in the elucidation of the electrosynthesis of benzanthrone and anthrone,[388] both important dye intermediates, and for analysis of these compounds in the catholyte and the raw products.

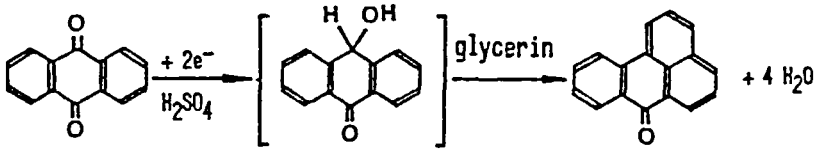


Figure 31 shows the reduction of anthraquinone recorded at 91.5°C at a rotating cylindrical carbon electrode with a surface of about 7 cm^2. The height of the voltammetric wave is a linear function of the anthraquinone concentration (Figure 32).

It may be useful here to make a remark concerning the use of polarography and voltammetry in connection with electrosynthetic work. As stressed by Zuman,[389] great caution must be exercised by proceeding from mechanistic investigations based on polarography and voltammetry to a project in electrosynthesis on a macroscale. Mechanistic studies, which should precede synthetic work, are often carried out with the use of microelectrodes. i-E curves with such electrodes often differ from those with macroelectrodes. Hence, the i-E curve should be recorded with the electrode intended to be used for synthetic work, as shown in Figure 31, before the potential for the electrolysis is chosen.[195] For further examples, the reader should consult References 390 and 391.

a. Simultaneous Determination of Anthraquinone (I) and Benzanthrone (II)

Anthraquinone (I) and benzanthrone (II) can be determined simultaneously by polarography.[165,392,393] Figure 33 shows the sampled d.c. (curve 2) and the differential pulse polarogram (curve 1) of anthraquinone and benzanthrone in 15% v/v sulfuric acid in 75% methanol. As little as 0.05% of compound (I) can be determined in distilled benzanthrone

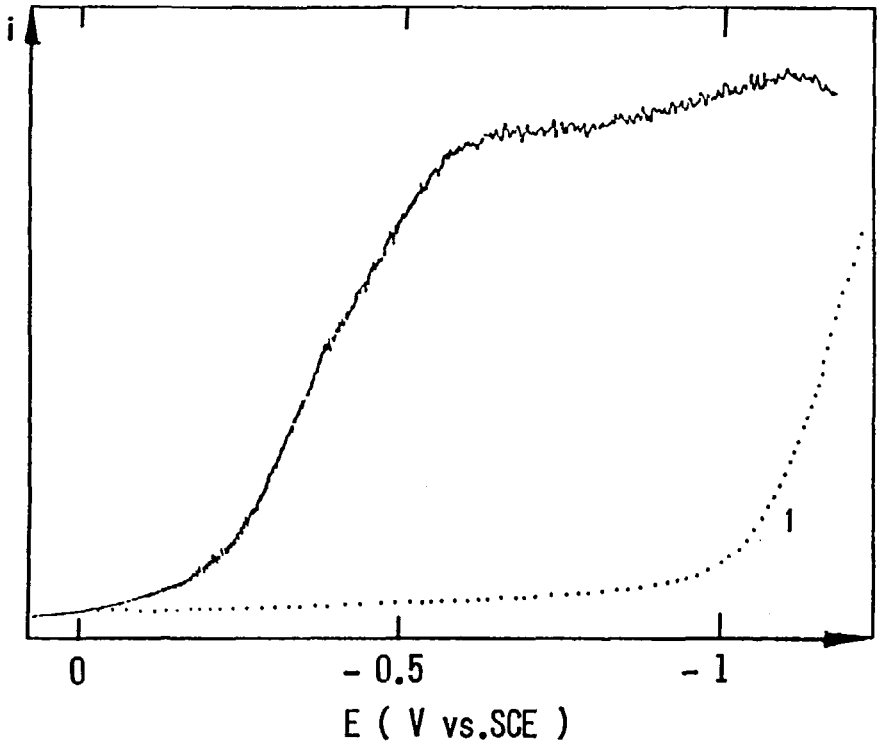


FIGURE 31. D.c. voltammogram of anthraquinone [50.8 g in 1000 mℓ concentrated sulfuric acid (d_{20C} = 1.801)] recorded at a rotating carbon cylindrical electrode at 91.5°C. Curve 1 = supporting electrolyte.[115]

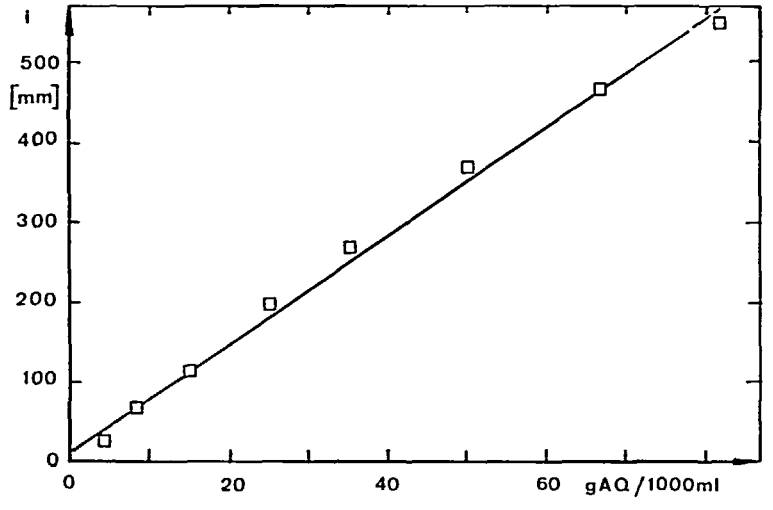


FIGURE 32. Height of the anthraquinone reduction wave (i_d) as a function of the anthraquinone concentration.[115]

by d.p.p. The d.p.p. assay is thus more sensitive for the residual compound (I) than chromatography.[115]

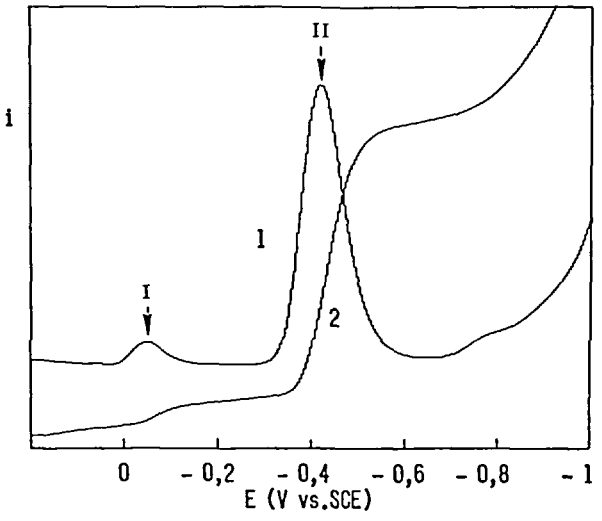


FIGURE 33. Differential pulse (1) and sampled d.c. polarogram (2) of a benzanthrone reaction mass containing 7% anthraquinone, measured in 15% v/v sulfuric acid with 75% methanol at 23°C. Wave (I) corresponds to the reduction of anthraquinone, wave (II) of the reduction of anthrone.[115]

b. Polarographic Determination of Anthrone and Anticipated Reduction Products from Electrosynthetic and Catalytic Reduction of Anthraquinone

The following compounds can be expected to occur as reduction products of anthraquinone and anthrone.[394]

Anthraquinone	(I)	395, 396
Hydroquinone	(II)	
Oxanthrone	(III)	
Anthranol	(IV)	
Anthrone	(V)	395—398
Bianthrone	(VII)	399—402
Dianthranol	(VIII)	403
Dianthrone	(IX)	400, 404
Anthrapinacol	(X)	
9,9'-Dianthranyl	(XI)	405
Anthracene	(XII)	405
9,10-Dihydroanthracene	(XIII)	(XHI[405])
hydrogenated in the aromatic nucleus and other compounds;		

All compounds listed here are polarographically active and their behaviors at the DME — with the exception of the anthrapinacol (X) — are described, or at least mentioned, in the literature. Among these products, anthraquinone (I) and anthrone (V) were determined routinely in crude anthrone samples from electrosynthetic and catalytic experiments[115] (Figure 34).

For the simultaneous determination of anthraquinone and anthrone, a supporting electrolyte consisting of ammonium chloride in glacial acetic acid was used;[395] for the assay of mixtures of anthraquinone, anthrone, and anthracene, 0.05 *M* tetralkylammonium-iodide either in methanol[395,396] or in DMF[396] are used. Differential pulse polarographic data of crude anthrone samples can be compared well with HPLC data, as shown in Table 10A. The reproducibility

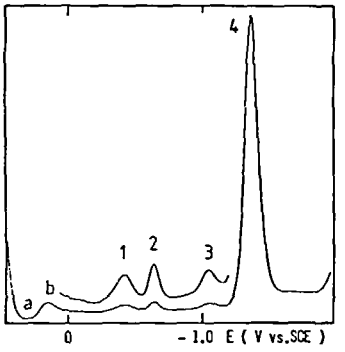


FIGURE 34. Differential pulse polarograms of crude anthrone in 0.05 *M* tetraethylammonium perchlorate in methanol. (a) Full-scale sensitivity = 20 μA. (b) Full-scale sensitivity = 5 μA. (1) Unidentified impurity; (2) 2.2% anthraquinone; (3) 1.7% dianthrone; (4) 91.3% anthrone. D.p.p.: drop time 1 sec, scan rate 5 mV sec^{-1}; pulse amplitude −25 mV.[115]

Table 10A
COMPARISON OF DIFFERENTIAL PULSE POLAROGRAPHIC AND HPLC DATA OF ANTHRAQUINONE, DIANTHRONE, AND ANTHRONE IN CRUDE ANTHRONE SAMPLES

	Anthrone (w%)		Anthraquinone (w%)		Dianthrone (w%)	
Sample	d.p.p.	HPLC	d.p.p.	HPLC	d.p.p.	HPLC
1	94.1	93	4.8	5.9	2.1	1.3
2	75.3	76.6	25.5	21.2	1.3	1.2
3	86.4	87.8	10.7	9.1	2	1.2
4	91.7	90.3	9.5	7.2	1.9	1.4
5	84.6	95.5	8.5	7.5	2.1	2.1
6	89.9	91.7	1.0	1.0	1.9	2.6
7	60.7	59.1	24.4	27.9	4.7	2.7
8	17.9	16.4	75	42.3	4.1	3.0

of the method[115] is summarized in Table 10B. We considered the reproducibility level of ±39% for the dianthrone to be acceptable for this crude material.

c. Dianthrone (IX), Dianthranol (VIII), Bianthrone (VII), and 9,9′-Dianthranyl (XI)

Dianthrone (IX)[400,404] (Figure 35) and sennosides,[406] present in a few percent in rhubarb, show irreversible two-electron waves, which are ascribed to the cleavage of the C-C bridge to the anthrone (V) and reduction of the carbonyl to the corresponding alcohol [dianthranol (VIII)], which seems to be dehydrated to the corresponding 9,9′-dianthranyl (XI).

Dianthranol (VIII) forms a reversible redox system with the corresponding dehydrodianthrone.[403] The product of the macroscale electrolysis of the latter product at a large cathode behaved identically to dianthranol.

In the d.p.p. of a methanolic solution of adduct of dianthranol and 2-propanol (added to stabilize the compound), a well-formed oxidation wave at +240 mV vs. SCE and a small wave at −850 mV vs. SCE were observed.[115] The latter was identified as corresponding to the reduction of bianthrone (VII) (Figure 36).

Table 10B
REPRODUCIBILITY OF THE DIFFERENTIAL PULSE POLAROGRAPHIC DETERMINATION OF ANTHRONE, ANTHRAQUINONE, AND DIANTHRONE IN A SAMPLE OF CRUDE ANTHRONE

Measurement	Anthrone (w %)	Anthraquinone (w %)	Dianthrone (w %)
1	87.3	11.6	1.0
2	86.7	10.6	2.2
3	87.5	10.9	2.7
4	87.1	9.7	1.0
5	84.1	10.4	2.4
6	85.7	11.0	2.6
d.p.p.	86.4	10.7	1.98
RSD	±1.5%	±6%	±39%
HPLC	87.8	9.1	1.2

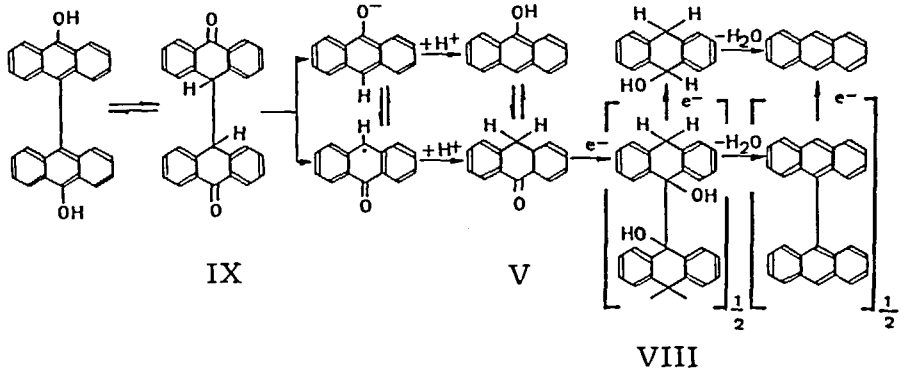


FIGURE 35. Reduction mechanism of dianthrone (IX) according to Asahi et al.[406]

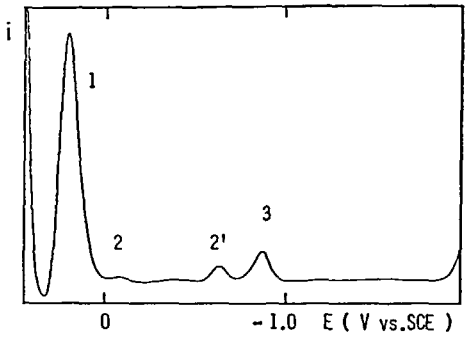


FIGURE 36. Differential pulse polarogram of dianthranol (VIII) in 0.05 *M* tetraethylammonium perchlorate in methanol. (1) dianthranol; (2,2') unidentified impurities; (3) bianthrone (VII).[115]

Polarographic reduction of bianthrone (VII), studied in some detail,[399-402,407,408] is accompanied by an equilibrium between two forms, A and B. The reduction of the A form proceeds in 0.1 *M* tetraethylammonium perchlorate in DMF in an irreversible ECE process in which

the initially formed A-like anion radical $A^{\cdot}$ rapidly twists to $B^{\cdot}$, which in turn rapidly reduces[407] to B^{2-}.

B. Dyes

Estimate of aggregation numbers from polarographic data — a less common application — is discussed first in this section, followed by a brief discussion of azo and triarylmethane dyes and food coloring matters.

1. Polarographic Determination of Aggregation Numbers of Dyes

The tendency of many dyes to associate in aqueous solutions has long been recognized.[409] It was suggested that dimerization and higher polymerization in aqueous systems is a universal property of organic dyes.[410,411]

Since almost all textile dyes are applied from aqueous systems, an understanding of the association of dyes in water is of importance in kinetic and thermodynamic studies of dying. There is, nevertheless, a lack of agreement about the nature of aggregation in solution and particularly about aggregate size.[412]

The polarographic method is said[413] to be much simpler and quicker than conventional methods such as light scattering, spectrophotometry, osmotic pressure, viscosity, electrical conductivity, or diffusion measurements, etc. The degree of association of dyes can be measured by polarography in presence of electrolytes over a wide range of dyes and electrolyte concentrations, and it can also be used to measure the changes in degree of aggregation with the temperature.[414] The polarographic aggregation numbers are said to be significant to about $\pm 10\%$[412] and to about $\pm 20\%$,[409] respectively. Polarographic results obtained[409,414,415] for dimers such as Methylene Blue and Orange® (II) are in good agreement with results obtained using conductivity and spectrophotometric methods.[416] The results of the anionic Congo Red® which forms aggregate containing up to many thousands of molecules[413] agree well with those of other techniques.[412] The aggregation number of the latter compound is very much affected by the presence of additives such as urea or formamide.[417]

The aggregation number (Z′) is obtained from the square root of the diffusion coefficient (D) calculated from the limiting current (i_d) with the help of the Ilkovic equation, using a cadmium salt of the same concentration as the dye as a standard and the empirical relation of Hillson and McKay.[413] This relationship was criticized by Storck et al.[418] in 1972. Criticized were (1) the simple relationship between the diffusion coefficient (D) and the molecular weight (M) irrespective of the shape of the molecule, which is theoretically unsound; (2) the number of electrons involved per monomeric unit was set for the calculation of the aggregation number (Z′) equal to two in all cases; (3) the possibility that adsorption of the dye at the mercury may affect the value of i_d was not taken into account, although the authors had found a reduction of the interfacial tension of the mercury by the dyes. It is problematic[191] how the association in the vicinity of the electrode relates to that in the bulk of the solution. Although the principle has thus been queried, polarography has since been used to determine aggregation of anionic dyes in aqueous solutions[416] of Solochrom mordant dyes (Solochrom Yellow 2 GS, Red ERS, Black WDFA, black PVS),[415] etc. The polarographic values agree well with spectrophotometric data (see, e.g., Reference 415). The influence of increasing hydrophobic character caused by the increasing length of alkyl chains which promotes aggregation, and the number and position of the hydrophilic sulfonate groups on the aggregation of monazo acid dyes, were also studied.[412]

Good agreement[115] for simple, very pure dyes, such as Congo Red®, with data reported in the literature was found. With commercial products, the main reason for the failure of such measurements are the presence of impurities. Purification of such products is still difficult.

2. Azo Compounds and Azo Dyes

The majority of papers dealing with azo, azoxy, and diazo compounds is restricted to the discussion of mechanisms of their reduction.[419,420]

For four azo dyes of biological importance — CI Direct Orange 34, CI Acid Red 73, CI Direct Blue 84, and CI Direct Red 80 — the best-developed peaks for quantitative d.p.p. analysis were found in a Britton Robinson buffer, pH 3.4, or in 0.05 *M* sulfuric acid. Ranges of concentration for linear response are from 3×10^{-5} to 5×10^{-7} *M*.[421]

Azosalicylic and *o,o'*-dihydroxyazo dyes are among the most important azo dyes applied either directly or with the aid of a suitable mordant in the dying of textile fibers.[415,422] From the analytical point of view, azo dyes are very valuable for trace analysis of rare metals like zirconium, cerium, thorium, etc. Due to their wide use in industry as textile dyes, coloring agents in foods, and in pharmaceuticals, they become environmental polluants through the discharge of chemical and textile work effluents into rivers, especially if the waste waters are not treated,[423] but also through intake of certain foods and drugs that contain azo compounds.[421] In this context, concentration changes of commercially used diazo dyes (Acid Red 73, Direct Blue 84, Direct Red 24, Direct Orange 34) were monitored by differential pulse polarography in mini-aquaria containing plants and animal life.[424] The four dyes were added at 10^{-4} *M*, a concentration thought likely to be discharged into an effluent. The most toxic dye (Acid Red 73) in the series is also the easiest to reduce polarographically, showing a reduction wave at −0.18 V vs. SCE, in formate buffer, pH 4. The toxicity could be related with the metabolic reduction of the azo group to yield toxic aromatic amines, a process analogous to that which occurs in polarographic reduction.[425-428]

Various attempts have been made to correlate polarographic data and physiological activity. Correlation of physiological activity with half-wave potentials indicates that the chemical reactivity is the predominant factor governing the physiological activity, whereas the lack of correlation is an indication that the role of transport might be predominant.[346] An example of the latter type is the behavior of some carcinogenic amino azo dyes, which show no significant correlation between half-wave potential and carcinogenic potency against rat liver.[429,430]

a. Azo Chelates

Azo dyes with two donor groups in ortho position to the azo linkage are powerful chelating agents. In the presence of metal ions, they exhibit two reduction waves one due to the free dye and the other to the metal-dye complex.[431-434]

Polarography can be used for the determination of azo dyes and their Cr, Co, and Cu complexes and cationic metallic species[435,436] in industrial effluents of dyestuff plants.[115] Polarographic techniques were used to follow complex azo dyes which are often not amenable to conventional waste water treatment processes, uncomplexed azo, as well as the free ionic toxic metals in waste waters from production plants.[115] Thus, electrochemical methods currently provide a very promising approach to environmental pollution monitoring, as they are capable of measuring a wide range of toxic species, ranging from heavy metals to organics including ligands at levels down to and below the parts per million level.

3. Triarylmethane and Phthalein Dyes

Polarographic and voltammetric studies of triarylmethane[437-443] and phthalein[444-446] dyes so far have been restricted to mechanistic studies, even when observed waves are often suitable for analytical applications.

4. Polarographic and Voltammetric Determination of Food Coloring Matters

Color is to some extent self-limiting and no official limits are set on amounts of coloring matters that can be added to foods. The widespread use of coloring matters has aroused interest in their determination in food. Established analytical methods of identifying food

coloring matters are thin-layer chromatography, which is difficult to carry out quantitatively, and HPLC.[447] However, both generally require separation of the colors from even simple food matrixes.

On the other hand, direct determination of the mixture of Sunset Yellow FCF and tartrazine, tartrazine-Green S, Amarant and Green S in soft drinks such as orange, lime, and black currant drinks,[447] as well as of Chocolate Brown HT (declared 62.8 ppm, determined 61.7 ppm), Green S (declared 2 ppm, found 1.96 ppm), and tartrazine (declared 20 ppm, found 20.3 ppm)[448] is feasible directly by polarography without the need to separate the dyes.

Tetraphenylphosphonium chloride was shown to shift the peak potentials of tartrazine to a more negative potential at pH 9 and to enhance its peak height. This allowed mixtures of tartrazine and Sunset Yellow FCF to be determined simultaneously. The phosphonium ion suppresses the peak currents of certain coloring matters, e.g., Green S and Chocolate Brown HT at pH 9, thus allowing the determination of tartrazine in their presence.[449] A pH of 7 was chosen for the simultaneous determination of Red 2G ($E_{1/2} = -0.59$ V vs. SCE) and Red 10 B ($E_{1/2} = -0.8$ V vs. SCE) in presence of 600 ppm tetraphenylphosphonium chloride. Without addition of the phosphonium ion the peak potentials of Red 2G and Red 10 B at pH 7 were -0.66 and -0.77 V, respectively.[450] The recommended procedure allows the determination of the deacetylation of the azo Red 2 G during food processing. The procedure is limited to concentrations of food color not much above 5 ppm.

Anodic linear sweep voltammetry at a stationary glassy carbon electrode proved to be superior for the determination of certain food dyes,[451] while normal pulse voltammetry was in most cases found to be useless. In Britton Robinson buffer pH 2, most of the food colors give in LSV well-defined peak-shaped waves, the peak height being proportional to the concentration. Linear anodic peaks of synthetic food coloring matters at a stationary carbon paste electrode are generally sharper, better resolved from the cut-off current, and have lower baseline currents than those obtained at a glassy carbon electrode.[452] However, the more limited negative potential range available with carbon paste restricts the number of food colors which can be determined with this electrode.

Carbon paste and glassy carbon electrodes used as anodes in wall-jet configuration gave low limits of detection with rectilinear calibration graphs by flow injection analysis.[452]

XI. POLYMERS AND PLASTICS

Compared to the late 1960s and 1950s, the number of practical applications of polarographic and voltammetric methods to the analysis of polymers and plastics have become more limited, especially in the West. While modern polarographic methods have contributed to a beter understanding of biopolymers,[453] they have apparently not kept the popularity in the analysis of synthetic polymers.[454]

The practical value of polarography for the analysis of various polymer-monomer systems and for determining additives and impurities has been recognized in Russia and Eastern European countries and is still practiced there.[366,455-459]

Many organic compounds used both as raw materials and as auxiliary substances in the manufacture of plastics are amenable to polarographic and voltammetric determination. The products of reactions yielding polymers contain some of these substances either as unreacted monomers or as residual polymerization initiators, either in low quantities or as structural units of macromolecules. Many additives which are polargraphically active are essential constituents of plastic materials[366,456,460] such as

1. Catalysts, e.g., aromatic peroxides, aliphatic peroxides, tertiary amines, aliphatic azo compounds
2. Inhibitors, e.g., hydroquinones, butylated hydroxyanisole, *p*-tert.butyl phenolsulfide, *N*-phenyl-β-naphthylamine

3. Stabilizers, e.g., phosphite esters, alkylated phenols, benztriazoles, di-butyltin-dilaureate
4. Initiators, e.g., amines, bisazoisobutyronitrile
5. Plasticizers, e.g., dialkylphthalates, alkyl- and aryl-phosphates
6. Chain transfer and cross-linking agents, e.g., mercaptans, organic peroxides, alkylphthalates, di-isocyanates
7. Flame retardants, e.g., halogenated organics, Sb_2O_3

Polarographic and voltammetric analysis offers numerous applications, particularly in quantitative analysis, for (1) the purity of raw materials; (2) the inhibitor content of monomers; (3) the residual monomer content of polymers and plastics; and (4) the additive content of the product of the reaction mixture, but also for effluents from production facilities. Occasionally, these techniques can be used for qualitative analysis of such samples as well.

Suppression of the maximum of the first kind or preferably of the copper maximum of the second kind has also been proposed for the analysis of polymers.[461] The method was used in routine determination of molecular weights of a wide variety of polymers.[366,455] Similarly, the molecular weight of poly(methacrylic acid) was estimated from the suppression of the oxygen maximum.[462] The determination of free formaldehyde in urea resins using the suppression of the oxygen maximum at a pyrographite electrode in 0.3 *N* Na_2HPO_4 medium[463] could not be replicated in our laboratory.[115]

A. Examples of Qualitative Polarographic Analysis of Polymers and Plastics

Pyrolysis under controlled conditions followed by the detection using GC or GC-MS is nowadays generally used for the qualitative analysis of polymers.

Polarographic identification is based on pyrolysis of polymers in which mainly vinyl monomers and some other components containing $\rangle C = C \langle$ double bonds are formed, which can be carried out using direct or indirect polarographic determination after bromination[366,368] or nitration.[366] The major degradation products of methacrylate and styrene polymers were found to be their respective monomers, such as styrene, methyl methacrylate, and acrilonitrile, which all are reducible at the dropping mercury electrode.[456]

B. Examples of Quantitative Polarographic and Voltammetric Assays

1. Monomers

Successful practical applications have been described for the polarographic determination of minor quantities of monomers, such as styrene, methyl methacrylate, acrylamide, acrylonitrile, aldehydes, isocyanates, and anhydrides.

A practical example is the polarographic determination of low concentrations of methyl metacrylate, styrene, vinyltoluene, and vinylxylene (0.2 to 0.5 mg ℓ^{-1}) and of polymerization initiators such as azodiisobutylnitrile (0.2 to 5 mg ℓ^{-1}), benzoyl peroxide, cyclohexylperoxidicarbonate, and laurylperoxide (0.2 to 15 mg ℓ^{-1}) in effluents from polymer production after extraction. For the determination of the monomer extracts, a mixture of benzene-DMF-water containing tetraethylammonium iodide was chosen. The half-wave potentials for the respective monomers were -2.01 V vs. SCE for methyl methacrylate; -2.28 V for styrene; -2.3 V for vinyltoluene; and -2.33 V for vinylxylene.[464] The very negative reduction potentials rule out the use of chlorinated hydrocarbons as solvents. In this potential range trouble with the working electrode — due to erratic dropping — is quite common, although seldom mentioned in papers. The use of the Smoler capillary with the tip in horizontal position improves curves.[191]

For nonreducible or nonoxidizable substances, indirect methods are used. Thus, vinylacetate in poly(vinylacetate) can be determined as acetaldehyde after hydrolysis with lithium hydroxide in aqueous ethanol;[366] phenol in chlorbisphenol C 1 (2,2-*bis*(4-hydroxiphenyl)1,1,1-trichloroethane) can be determined[367] by reduction of a *p*-nitrosophenol derivative in the nitrosation medium ($E_{1/2} = -0.55$ V vs. SCE). For the identification of various

polyamides, the polyamide was first hydrolyzed to amino acids which were converted into polarographically active Schiff bases by condensation with formaldehyde.[366]

a. Styrene

Styrene in polystyrene and its copolymers is determined either directly or, because of the highly negative value of the reduction potential, indirectly as its pseudonitrosite.[366] The following reaction is used:

$$C_6H_5CH{=}CH_2 \xrightarrow{HNO_3} C_6H_5{-}\underset{NO}{CH}{-}\underset{NO_2}{CH_2}$$

Treating styrene with $NaNO_3$ in acetic acid gives mixtures of $PhCH(NO)CH_2(NO_2)$ and $PhC(:NOH)CH_2NO_2$. Comparison with $PhCH_2CH_2NO_2$ shows that the NO_2 group is reduced. This technique was employed for the determination of styrene in samples of polyester laminates and acrylic polymer dispersions.[369]

b. Methyl Methacrylate

Polarographic direct and indirect procedures similar to those used for styrene have been extensively used for the determination of the monomer in acrylic polymers.

The direct d.c. polarographic determination of methyl methacrylate and other monomers in solution of acrylic-styrene copolymers was performed in an alcohol benzene mixture with tetrabutylammonium iodide supporting electrolyte.[465] The following half-wave potentials were found: Bu acrylate, −2.224 V; Bu-methacrylate, −2.214 V; methyl methacrylate, −2.245 V; methacrylamide, −2.39 V; styrene, −2.5 V vs. calomel electrode. The d.c. polarogram shows two waves; the first corresponds to the overall reduction of the acrylic compounds, the second to the reduction of the styrene (in DMF medium the second reduction wave of the methacrylamide overlaps that of styrene). For 20 replicates a variation of ± 10% is given compared to 11 to 20% for the GC method after preliminary thermal treatment. As little as 190 ppb methacrylate in 0.005 *M* tetrabutylammonium hydroxide can be determined by differential pulse polarography.[460]

c. Acrylamide in Polyacrylamide

The high chronic toxicity of acrylamide[466] has created the need for sensitive, rapid analytical techniques capable of detecting and determining this monomer in polymeric materials as polyacrylamide. Acrylamide polymers are used extensively at water treatment works to aid water clarification[467] and for conditioning sludges.

Numerous methods have been reported in the literature for determining acrylamide. Chromatographic — including gel permeation chromatography and HPLC — and polarographic methods are among the most commonly used (see References 467 and 468 and references therein).

The polarographic behavior of acrylamide is well documented.[469-476] Betso and McLean[468] applied d.p.p. to the determination of the acrylamide monomer in polyacrylamide; possible and actual interfering compounds and their removal were studied. The procedure is essentially a modification of the classical d.c. polarographic method.[477] The detection limit of the monomer for the d.p.p. method is less than 1 ppm. In comparison, the detection limit of HPLC is about 0.2 ppm in natural and polluted aqueous environments.[467]

A differential pulse polarographic procedure involving the preliminary extraction of the monomer is used routinely[115] to determine traces of acrylamide higher than 1 ppm in polyacrylamide production intermediates using a methanolic solution with phosphate-citric acid buffer,[478] pH 2.2,or a methanolic solution with tetrabutylammoniumhydroxide as supporting

electrolyte.[468] The reduction peak in both cases is well defined and well resolved from the background.[115]

A derivative d.c. polarographic method was proposed for the determination of acrylamide and unsaturated dicarboxylic acids or their salts, such as sodium maleate, in the same sample using the aforementioned phosphate-citric acid buffer as supporting electrolyte. Polyacrylamide, acrylamide-based copolymers, and initiators such as ammonium persulfate do not interfere.[478]

d. Acrylonitrile

Improved methodology for the determination of acrylonitrile is needed because of its toxicity and purported carcinogenic properties.[479] Acrylonitrile is extensively used in industry, e.g., in the manufacture of fibers, elastomers, resins, latex, and in synthesis of other chemicals, primarily adiponitrile and acrylamide. Polymers containing acrylonitrile monomers are used for packaging household articles designed for foodstuffs.[480]

Most recent procedures for determination of acrylonitrile[479] utilize gas chromatographic detection with FID detector.[481] Due to poor specificity of this detector, it may be difficult to detect low levels of acrylonitrile in the presence of other species, and therefore either long GC analysis times or identification of the peak by GC-MS is required.[481]

Polarography of acrylonitrile is well documented. Several papers discuss the polarography in general,[482-485] as well as the determination in polymeric systems or in waste waters.[486] Sodium, potassium, and ammonium salts are eliminated by extraction with benzene. The recovery after one single extraction is said to be about 96%. The method is applicable to industrial wastes containing 3 to 5 mg ℓ^{-1} of the monomer. Used as supporting electrolyte is 0.05 *M* tetraethylammonium iodide in 90% DMF. For routine polarographic determination of low concentrations of acrylonitrile in resins, we use[115] a method adopted from the procedure described by Daues and Hamner.[487] The sampled d.c. reduction wave and the d.p.p. wave in 2.3 m*M* tetrabutylammonium hydroxide in methanol containing 6% water as supporting electrolyte are well developed with a half-wave potential at -2.2 V vs. SCE. The recovery of added acrylonitrile in the procedure using azeotropic distillation for the separation from other components is of the order of 90 to 95%, with a lower detection limit of about 10 to 15 ppm. A method for the d.p.p. assay of acrylonitrile in aqueous extracts, which involves also azeotropic distillation with methanol, has been recommended by the FDA.[480]

e. Miscellaneous Monomers: Aldehydes, Isocyanates, Anhydrides

Further monomers which can be determined by polarography include aldehydes which are components of commercially important phenolic and amino resins, as well as isocyanates as unreacted monomer (phenylisocyanate, 2,4-tolyene diisocyanate), and as end groups incorporated in polymers. Polarography is one of the few methods capable of determining both simultaneously.

Prolonged exposure to even very low atmospheric concentrations of toluene diisocyanate may cause death,[488] thus making improved methods for its determination an urgent goal. A rapid method of determination of this monomer in air is based on high-performance liquid chromatography with amperometric detection in the oxidative mode after derivatization of the electrometrically inactive toluene diisocyanate with *p*-aminophenol. *p*-Aminophenol in 0.05 *M* Na_2HPO_4, 30% acetonitrile at a 15% Kelgraf electrode, exhibits one anodic wave at $+0.38$ V and one reduction wave at $+0.27$ V. Addition of toluene diisocyanate to *p*-aminophenol solution gives rise to two new oxidation peaks at $+0.51$ and $+1.15$ V vs. Ag/AgCl/ 3.5 *M* KCl. Disadvantage of this approach is the formation of multiple derivatives which might lead to somewhat more complex chromatograms than those obtained with existing methods applied to mixed isocyanate atmospheres. The principle advantage, however, is considerably reduced sample handling prior to the chromatographic step without

significant sacrifice in sensitivity. As detection limit, 94 pg of toluene diisocyanate injected is given.

The determination of unreacted anhydride in polymers is often a difficult problem, as the resins always contain free carboxylic groups on the polyester molecule and also free low-molecular acids, which both interfere with the common acidimetric method.[366] Experiments carried out in the author's laboratory[115] showed a well-formed differential pulse polarographic wave for the unreacted maleic anhydride in a solution of 0.1 *M* tetraethylammonium perchlorate in a mixture of benzene and acetonitrile (3:2), with a peak potential of about −0.85 V vs. SCE and a linear dependence of peak height on concentration in the range from 20 to 120 μg polarographed solution. The nonaqueous electrolyte prevents hydrolysis of the anhydride and thus permits direct assay of the polyester resin. The mono- and diester can be determined simultaneously as the monoester has a peak potential of −1.05 V and the diester of −1.35 V vs. SCE. An alternative to the direct method is to hydrolyze the maleic anhydride to maleic acid, which is polarographically active.[489]

2. *Additives: Quinones, Phenols, Organotin Compounds, Antioxidants, Hydroperoxides*

a. Stabilizers, Inhibitors

Technical acrylonitrile often contains traces of stabilizers, e.g., *p*-methoxyphenol. Results for assays[115] using anodic differential pulse voltammetry at a stationary glassy carbon electrode in a solution of 0.12 *M* sulfuric acid in a mixture of benzene and ethanol agreed well with the value of 40 ppm given by the manufacturer.

Differential pulse voltammetry is used to monitor phenolic and amine catalysts and inhibitors in resin educts, such as *p*-tert-butylcatechol in styrene, or hydroquinone and *p*-methoxyphenol in methacrylic acid, but also of phenols and amine additives in various resins (e.g., Epocryl 322, Derakane, etc.). As commercial manufacturers usually use different additives, the origin of the product can easily be identified. Phenothiazines, e.g., form two well-shaped anodic pulse voltammetric waves at a stationary glassy carbon electrode in a solution of 0.12 *M* sulfuric acid in a mixture of ethanol and benzene (2:1). Both waves show linear dependence of the peak height on concentration in the range from 20 to 200 ppm of Derakane.[115] The reactions of inhibitors (*p*-benzoquinone and hydroquinone) during storage of methyl methacrylate have also been investigated by polarography.[458]

b. Organotin Compounds

Organotin compounds have found widespread use as stabilizers for PVC plastics, but also as rubber antioxidants, as Ziegler-type catalysts in the polymerization of olefins, as active ingredients in certain veterinary medicines, as wood preservatives, as fungistate in paper, textile, and polyvinyl paint manufacture, and as fungicides in agriculture.[490,491] The most important preparations used in the plastic industry are based on dialkyltin compounds (R_2Sn), especially with butyl and octyl groups.

Organotin compounds are reduced directly at the dropping mercury electrode.[490-494] The introduction of organotin compounds with alkyl groups smaller than C_4 causes a serious safety problem due to their toxicity.[495] Markusová and *Žežula[496] studied the polarography of trimethyl tin chloride in aqueous 0.1 *M* KCl or Britton Robinson buffer solutions. D.p.p. measurements demonstrated that small amounts (0.5 to 2%) of $(CH_3)_3SnX$ can be determined in $(CH_3)_2SnX$. Of 12 supporting electrolytes tested, only 0.1 *M* $LiClO_4$ in ethanol was useful.[115]

The electrochemical determination of multicomponent mixtures containing trace amounts of organotin compounds was shown to be best carried out by combination of HPLC and electrometric determination.[497,498] Mixtures of tributyl tin, triethyl tin, and trimethyl tin cations were separated on a Whatman PXS cation-exchange column using as mobil phase 60% ethanol in water, 0.042 *M* sodium acetate, pH 3.3, prior to differential polarographic assay.

Differential pulse detection can provide in certain cases a useful extension of the simple amperometric electrochemical detection combined with HPLC, e.g., when the selectivity of the latter is inadequate. On the other hand, it is generally accepted that the limit of detection using the differential pulse technique is equal or up to 20 times poorer than that of simple amperometric detection.[499]

The triphenyl tin radical formed during reduction adsorbs strongly at the mercury electrode. This effect was used to determine this compound by stripping voltammetry at a rotating mercury-coated platinum wire electrode at concentrations down to 10^{-8} *M*. A procedure has been developed for determining triphenyl tin compounds in potato crops.[500]

Polarographic methods can be also used for determination of organotin compounds in plastics. Thus, Bork and Selivokhin[501] determined organotin compounds in PVC, and Shkorbatova[502] applied d.c. and a.c. polarography to the analysis of effluents and polymers containing trialkyl-substituted organotin compounds.

Differential pulse polarography was used for determination of organostannic compounds leached into aqueous medium from antifouling paints containing organostannic copolymers. The species liberated was identified[503] as the cation Bu_3Sn^+.

Polarography was used for the determination of residual tin in polyurethane foams prepared with tin catalysts such as tin octanoate after extraction.[504] Determination is carried out by means of standard additions of tin(II)chloride or tin octanoate. The sensitivity given is 0.01%. The author used polarography for the determination of tin in tin octanoate samples.[115]

c. Antioxidants

Critical appraisal of published procedures for the determination of antioxidants in polymeric materials cites 15 polarographic and voltammetric papers.[505] The analytical problems arise from three factors: (1) since the antioxidant is in a more or less insoluble matrix, a prior separation of the antioxidant is in most cases a prerequisite; (2) the high reactivity and low stability of antioxidants. Once they have been isolated, there is no lack of methods for their estimation, due to their high reactivity; and (3) the low concentration of antioxidants present (0.01 to 1%).

In a recent survey of analytical methods for the determination of antioxidants (stabilizers) in plasts, the chronopotentiometric technique proposed by Ward[507] using ethanol and acetonitrile as solvents and a parafin wax-impregnated carbon electrode, was quoted.

The use of differential pulse voltammetry at a glassy carbon electrode for the determination of Irganox 1010[508,509] or tetrakis[methylene-3-(3′,5′-di-t-butyl-4′-hydroxyphenyl)proprionate]methane induced[510] further electrochemical investigations of a number of commercially available high-molecular-weight hindered phenols used as antioxidants and stabilizers. The detection limits are in the range of 1.3 to 8.2 ppm. Cyclic voltammetry and d.p.v. showed that the oxidation of these phenols in neutral or acidic media is accompanied by film formation. In alkaline media filming can be avoided (the phenoxide being oxidized electrochemically to the corresponding stable phenoxy radicals), but the detection limits are considerably higher, with values ranging from 28 to 50 ppm. Irganox 1076 was shown[115] to yield a well-formed anodic wave on glassy carbon in an aprotic supporting electrolyte, so that an electrometric detection following HPLC should be feasible.

d. Peroxides, Hydroperoxides

Organic peroxides and hydroperoxides used as catalysts and polymerization initiators are determined by polarography in a wide range of resins, such as acrylics, polyesters, styrene, and butadiene latexes.[366] Lebedeva et al.[456] have listed half-wave potentials and conditions for polarography, such as solvents and supporting electrolytes for 20 different peroxide and hydroperoxide catalysts.

A recent practical example is the polarographic determination of *p*-(chloromethyl)benzoyl

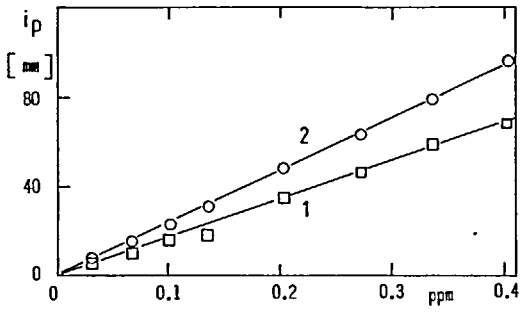


FIGURE 37. Calibration curve for atrazine, recorded in 0.1 *M* HCl, 0.5 *M* NaCl. (1) Peak height (i_p) of the first wave; (2) i_p of the second wave.[115]

peroxide and the corresponding acid in a low molecular weight polymer after its extraction with DMF.[511]

e. Varia

In the field of epoxy-resins cross-linking agents such as mono- and dicarboxylic acid derivatives containing nitrogen[512] and free phenolic hydroxyl groups[513] were determined amperometrically at a rotating platinum electrode.

Amperometric titration was proposed for the assay of 2-benzothiazole sulphenamides, which are widely used as rubber accelerators in industry.[514] The amperometric results are obtained within 5 min, and are — for bentothiazole sulphenamide contents of 0.5 to 4 mg — correct within ±2%.

Polarographic and voltammetric studies describe the reduction of vinologous carbonic acid chlorides,[515] the quantitative assay of *N*-chlorocarboxamide groups in polymers,[516] and the average methylene group content of amino resins.[517]

XII. AGROCHEMICALS

Analysis of agrochemicals involves determination of pesticides, herbicides, fungicides, metal complexes, organochlorine, organophosphorous, nitro- and sulfur-containing compounds, carbamates, ureas, and heterocyclic nitrogen compounds.

The determination of agrochemicals in formulations and of residues and their metabolites in the environment is a complex and highly technical field in which sampling, sample preparation, sample clean-up, etc. provide substantial challange. The analysis of residues is mainly complicated because these substances occur mostly in very low concentrations of the order of 1 to 100 ppb. Reliable sensitive analytical methods are needed.[278]

One of the reasons for the limited use of polarography in monitoring agrochemical residues and their metabolites in the environment was the inadequate detection limits of conventional d.c. polarographic methods.[518] With the development of GC methods in the 1960s offering higher sensitivities than d.c. polarography it is not surprising that the polarographic methods have been increasingly ignored.

Modern instrumentation and modern techniques of the 1970s have provided the technical and scientific basis for the development of methods for trace and ultratrace agrochemical determination suited to real problems of practical analysis. The detection limit of carbaryl (1-naphthyl-*N*-methylcarbamate), e.g., was lowered from 2 μg $m\ell^{-1}$ by d.c. to 0.2 μg $m\ell^{-1}$ by pulse polarography and to 0.05 μg $m\ell^{-1}$ after nitration of extracted samples.[362,373] Solutions of about 5×10^{-8} *M* of the herbicides diaquat and paraquat can be determined by d.p.p. in the eluate following sorption on a strongly acid cation exchanger and elution with saturated ammonium chloride.[519] Figure 37 shows[115] pulse polarographic calibration curves for atrazine in the range from 20 to 400 ppb.

Taking into account the high sensitivities offered by modern polarographic methods and the fact that about 75% of all herbicides used at present in agriculture can be directly reduced at the dropping mercury electrode,[363] it is surprising that so few working methods have appeared in the recent literature. This is reflected in the limited number of polarographic applications cited in official manuscripts, such as the *Pesticide Manual* of the British Crop Protection Council 1979,[520] or in periodical series such as the *Residue Reviews*[521] or *Analytical Methods for Pesticides and Plant Growth Regulators*.[522] In the last volume of *Updated General Techniques and Additional Pesticides* (Vol. 11, 1980),[522] the use of polarography is cited twice: (1) for the assay of fentin hydroxide (triphenyltin hydroxide) involving wet ashing of the fentin hydroxide followed by the determination of the inorganic tin by polarography or colorimetry;* and (2) for the analysis of *N*-nitroso compounds in pesticide formulations.

A comprehensive account up to 1970 of the electroanalysis of pesticides is given in the book by Nangniot (1970) *La Polarographie en Agronomie et en Biologie*,[523] review papers,[524-529] and particularly the recent ones.[105,373,530-534]

A. Examples of Polarographic and Voltammetric Determination of Chemicals Used in Agriculture

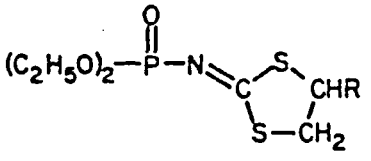
1. Herbicides, Pesticides, Fungicides

The most often used herbicides, for instance, are *s*-triazines, members of the 2,4-D family, propachlor, and certain carbamates.[535]

a. Azomethine-Containing Compounds; s-Triazines

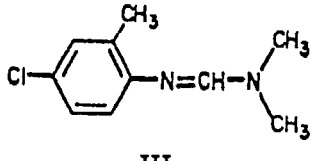
Considering the analytical usefulness of >C = N-reduction waves, relatively few published methods deal with the assay of azomethine-containing pesticides.

The study of polarographic behavior of the systemic insecticides Cyolane (I) and Cytrolane (II):

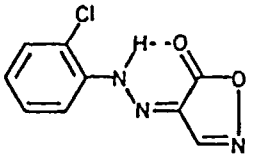


I, R = H
II, R = CH_3

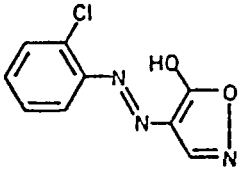
containing an extranuclear azomethione group conjugated to a heterocyclic ring system, Chlordimeform (III) (a broad spectrum acaricide and insecticide) and Drazoxolon (IV) (a highly active foliage fungicide) in aqueous solutions[536] offered possibility of their determination:



III



IVa



IVb

Polarographic determination of Drazoxolon in grain formulations provides a rapid and sensitive method, and shows no interference from nonreactive ingredients in the formulation,

* See Section XI.B.2.b., and Reference 500.

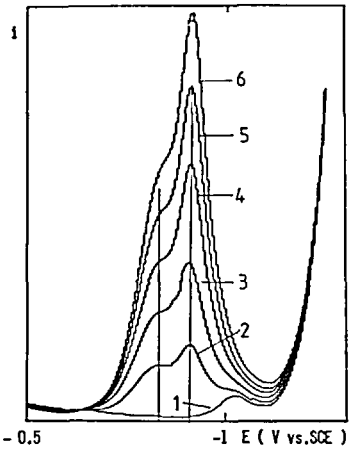


FIGURE 38. Differential pulse polarographic wave of atrazine in 0.1 *M* HCl, 0.1 *M* NaCl. (1) Supporting electrolyte; (2) +1.7 ppm; (3) +3.45 ppm; (4) +5.17 ppm; (6) +8.6 ppm atrazine. D.p.p.: drop time 1 sec; scan rate 5 mV sec^{-1}; pulse amplitude −25 mV; full-scale sensitivity 2 μA. Atrazine = 2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine.[115]

requiring no solvent extraction prior to analysis, as is the case for the colorimetric method previously described.[536]

Among the growing numbers of agricultural chemicals routinely used in weed control is atrazine (2-chloro-4-ethylamino-6-isopropylamino-*s*-triazine), first synthesized by Geigy. Among analytical methods[537,538] for determination of *s*-triazines, GC seems the method of choice, particularly for complex mixtures containing several triazines. Polarography of *s*-triazines, which has been extensively studied,[539-547,548-550] was successfully used[550] in the d.c. mode for determination of several *s*-triazines in wastewaters following extraction with methylene chloride. The lowest concentration detected by this procedure was 0.1 ppm. Similarity of half-wave potentials in buffers pH 1.2 to 1.3 prevented simultaneous determination of individual triazines when present in wastewaters.[115,550] The use of d.p.p., which was first reported to enable 0.1 to 20 ppm to be determined, can be improved[115] (Figures 38 and 39) using 0.1 *M* HCl to detection limits of 0.02 ppm (see Figure 37).

Recent adsorptive stripping voltammetric measurements[550a] showed detection limits of 1 ppb for prometryne and 0.18 ppb for ametryne, respectively, with standard deviations of 4.5 and 6.7. As in chloro derivatives of *s*-triazines, chlorine is reductively eliminated;[543,544] electrochemical behavior indicates the possibility of preparative electrochemical treatment of wastewaters containing chloro-*s*-triazines (cf. also Reference 551), as the dehalogenated product is assumed to be nontoxic.[535]

Andreeva et al.[551] studied the purification of wastewaters from triazine herbicide production on active carbon, by oxidative reduction by chlorine, electrochemical reduction, precipitation, and thermal degradation. The electrochemical runs were not very successful.

The oxidation of *s*-triazines in anhydrous acetonitrile at a rotating platinum electrode is difficult[552,553] and occurs only at very positive potentials. Differential pulse voltammetry of *s*-triazines yielded well-developed peaks with potential $E_p = +1.98 \pm 0.02$ V vs. SCE. The peak height proved to be a linear function of the concentration from 40 to 300 ppm.[115]

Using linear sweep voltammetry on a slowly dropping mercury electrode in 0.05 *M* borate buffer, pH 11, containing 0.5 *M* KCl, one rather large wave for hydroxy-*s*-triazines was found[115] with peak potentials in the range of −0.96 to −1.13 V vs. SCE, which offers a possibility for analytical applications.

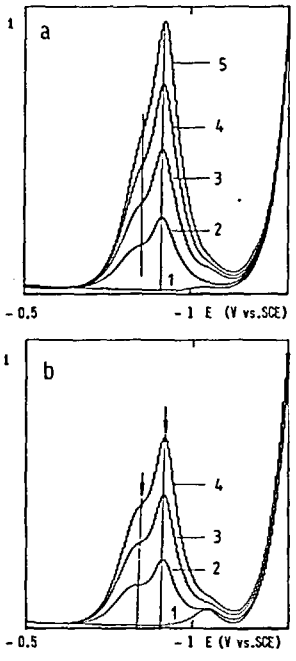


FIGURE 39. Differential pulse polarograms of (a) propazine in 0.1 *M* HCl, 0.1 *M* NaCl. (1) Supporting electrolyte; (2) +5.1 ppm; (3) +10.2 ppm; (4) +15.3 ppm; (5) +20.4 ppm propazine. (b) Of simazine: (1) supporting electrolyte; (2) +5.3 ppm; (3) +10.6 ppm; (4) +15.8 ppm. D.p.p.: drop time 1 sec; scan rate 5 mV sec^{-1}; pulse amplitude −25 mV; full-scale sensitivity 5 μA. Propazine = 2-chloro-4,6-di(isopropylamino)-1,3,5-triazine. Simazine = 2-chloro-4,6-di(ethylamino)-1,3,5-triazine.[115]

b. Chlorinated Herbicides, Pesticides, and Toxicants

A differential pulse polarographic method for the assay of residues of herbicides derived from 2,4-D (2,4-dichlorophenoxyacetic acid)* in irrigation waters was developed which is based on nitration of the extracted residue.[363] Optimum composition of the nitration mixture, the time of nitration, temperature, and pH were found to avoid oxidative destruction of the compounds as well as to obtain the highest sensitivity and the best discrimination between the studied compounds of similar structure. The detection limits of the d.p.p. procedure proposed are 30 μg ℓ^{-1} for 2,4-D and MCPA and 40 μg ℓ^{-1} for 2,4-DP and MCPP, and compare favorably with those of other analytical procedures,[363] such as spectrophotometry and GLC which require as GLC preceding methylation with diazomethane and has a detection limit of 50 μg ℓ^{-1}. Higher sensitivity of the d.p.p. method should enable its use for studying biological degradation of these substances in the soil.[363]

The method so far proposed for the determination of propachlor (2-chloro-*N*-2-propyl-acetanilide, also Ramrod or Bexton), based on determination of the total chlorine content, is neither specific nor sufficiently sensitive for determination of the compound in air. Therefore, a polarographic method was developed,[554] involving sampling by passing air through absolute ethanol or AFA filters. The alcoholic test solutions are diluted with an alcoholic solution of tetraethylammonium iodide to a concentration of 0.01 *M*, where a well-formed reduction wave ($E_{1/2}$ = −0.95 V vs. mercury pool) is formed. A linear dependence of the limiting

*Studied compounds: 2-(2,4-dichlorophenoxy)propionic acid (2,4-DP); 2-methyl,4-chlorophenoxy acetic acid (MCPA); 2-(2-methyl, 4-chlorophenoxy)propionic acid (MCPP).

current on concentration in the range from 2 to 15 μg $m\ell^{-1}$ was found with a relative error of 1 to 5%.

Highly toxic pentachlorophenol or its sodium salt has been used extensively as a pesticide, molluscicide, fungicide, bactericide, herbicide, and defoliant. It is lethal to many species of fish in concentrations above 0.2 ppm and produces a wide assortment of clinical symptoms in living organisms.[555] D.p.p. at the dropping mercury electrode and d.p.v. at the carbon paste electrode allow[555] the direct determination of pentachlorophenol at concentrations down to 0.3 ppm. The d.p.v. technique yields a well-formed oxidation peak, which can be used for the direct determination of pentachlorophenol. Furthermore, conversion of pentachlorophenol to chloranil and polarographic determination of the latter are feasible.[556] The analysis of liquid formulations such as: (1) containing 4.47% of pentachlorophenol in petroleum, (2) 32% in petroleum solvent plus emulsifier, (3) 7% in petroleum solvent, or finally (4) 6% in petroleum solvent together with an emulsifier and deionized water, is described.[557] Trichloro- and tetrachlorophenols and phenoxides can be determined[557] by d.p.v. at the glassy carbon electrode in 0.07 *M* sulfuric acid in methanol using anodic peaks with potentials in the range from +1.13 to +1.26 V vs. SCE, with detection limits between 0.5 and 3.4 ppm.

The electrochemical properties of picloram (4-amino-3,5,6-trichloropicolinic acid) and the related compound 3,6-dichloropicolinic acid (Dowco 290) were studied.[558] Under optimum conditions in 0.1 *M* Na_2SO_4 at pH 1.9 containing 1% 2-ethoxyethanol, the detection limit of the d.p.p. is given as 6×10^{-8} *M* for picloram and in 0.5 *M* sulfuric acid containing 5% 2-ethoxyethanol, 1×10^{-7} *M* for Dowco 290.

Linear sweep polarography allows determinations of hexachlorocyclohexane and of metaphos (*o,o*-dimethyl-*o*-(4-nitrophenyl)thiophosphate to levels of 10^{-8} and 10^{-9} *M* in natural waters.[518]

c. Carbamates, Thiocarbamates, and Ureas

Among 13 carbamate pesticides examined over the pH range from 2.5 to 10 at the glassy carbon electrode,[559] only Aminocarb (Matacil) and Zectran (Mexacarbate) yield well-formed voltammetric anodic waves, well resolved from the background with linear calibration plots in the range from 0.5 to 10 mg ℓ^{-1}. The estimated detection limit of the anodic differential pulse voltammetry is 30 μg ℓ^{-1}. Although the peak height is decreased by addition of methanol, a linear concentration response was still maintained, making electrochemical detection of HPLC effluents in 20 to 50% aqueous solutions of methanol possible. Pirimicarb and Methiocarb, which also show anodic signals at +1.15 and +1.2 V vs. SCE, respectively, compared to +0.65 for Zectran and +0.74 V vs. SCE for Aminocarb, are, however, not suitable for analytical electrochemical detection in combination with HPLC.

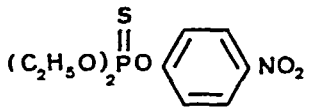
Carbamates and ureas (often classed in one group of compounds in pesticide analysis owing to their similar chemical structure[530]) usually give either ill-defined reduction waves or are totally nonreducible. Indirect polarographic determination after nitration or nitrosation has been reported.[362,364]

Pulse voltammetry permits direct determination of ethylene-bisdithiocarbamate fungicides such as Anthracol/Dithane S-60; and Dithane M-45 using 0.1 *M* NaOH in 50% ethanol.[560]

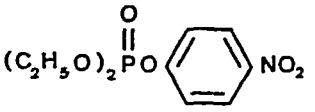
d. Nitro-Containing Pesticides

As noted in recent literature,[365] although there are many published methods for the determination of parathion, few offer sensitivity and convenience of polarographic methods.[365,523,527,561-564]

The polarographic behavior of parathion (V) and its major, highly toxic metabolites para oxon (VI) and *p*-nitrophenol



(V)



(VI)

and methyl parathion, *O*-ethyl-*O*-*p*-nitrophenylphosphonothioate and pentachloronitrobenzene were reexamined by normal and differential pulse polarography. D.p.p. can differentiate between parathion, *p*-nitrophenol, and pentachloronitrobenzene, but it cannot discriminate between the nitrophenylesters of related compounds. A hydrolysis procedure was worked out which allows the simultaneous determination of parathion and paraoxon, provided the latter is not present in greater than threefold excess in the range from 5×10^{-8} to 1×10^{-6} *M*, with a relative precision of ±8%. Trace determination of nitrophenylesters of related structures in mixture would require chromatographic separation prior to analysis.[365] Polák[568a] proposed d.p.p. for the determination of [2-(2-butyl)4,6-dinitrophenol] (dinoseb) and 2-methyl-4,6-dinitrophenol (DNOC) traces down to 0.02 μg/mℓ water for laboratories analyzing environment pollution.

2. Animal Growth and Feed Stock Additives; Food Analysis

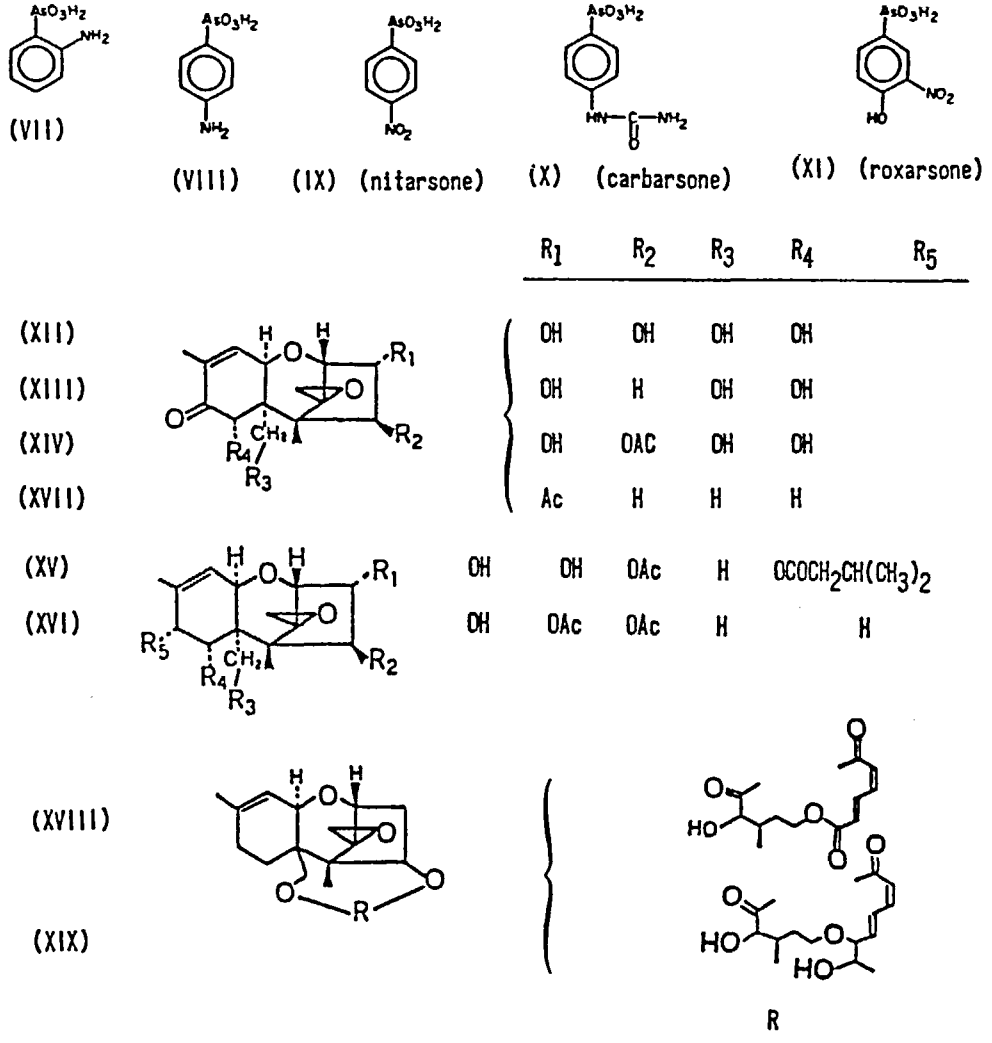
D.p.p. may be used for determination of organoarsenials (*o*-amino-(VII), *p*-amino-(VIII), *p*-nitro-(IX), *p*-ureidobenzene arsonic acid (X), and 3-nitro-4-hydroxybenzenearsonic acid (XI) down to 10^{-6} *M* levels. These compounds are widely used in agriculture, predominantly as animal growth promotors and feed stock additives. As the peak potentials are close together at −0.7 to −1.04 V vs. SCE in solutions containing hydrochloric acid and sodium chloride of pH 0.5 to 1.6, simultaneous determination is difficult without a separation step.[565]

The development of precise, selective, and sensitive methods for trichothecenes determination in naturally contaminated foodstuffs is of fundamental importance for environmental and health protection. A systematic investigation has recently been initiated by Palmisano et al.[566,566a] in order to assess the potentialities of d.p.p. as an accurate and sensitive means of determining this group of chemically correlated fungal metabolites characterized by high toxicity towards microorganisms, plants, animals, and humans.

Nivalenol (XII) (3α,4β,7α,15-tetrahydroxy-12,13-epoxytrichothec-9-en-8-one), deoxynivalenol (XIII) (3α,7α,15-tetrahydroxy-12,13-epoxytrichothec-9-en-8-one), and fusarenone-X (XIV) (3α,7α,15-trihydroxy-4-β-acetoxy-12,13-epoxytrichothec-9-en-8-one) can be determined in infected maize by d.p.p. following liquid/liquid extraction and chromatographic clean-up.[566a] Detection limits for the overall procedure and for a sample size of 50 g are of the order of 50 ng g^{-1}. The polarographic behavior of HT-2 toxin (XV), diacetoxyscirpenol (XVI), monoacetoxydeoxynivalenol (XVII), verrucarin-A (XVIII), and roridin-A (XIX) has been reported. Calibration graphs for representative toxins were obtained over the concentration range of 5×10^{-8} and 9×10^{-6} *M*.

Differential pulse polarography following an extraction procedure was applied to the determination of deoxynivalenol in Fusarium-infected corn.[566] Deoxynivalenol exhibits well-defined d.p.p. waves over a wide pH range. The best-suited wave for analytical purposes was obtained in Britton Robinson buffer, pH 8, with 10% methanol. A calibration graph was generated over the concentration range from 0.053 to 9.01 μ*M* by adding a standard solution of deoxynivalenol in methanol. A detection limit of about 50 ng g^{-1} (for a 50-g sample) was estimated.

According to Palmisano et al.,[566] polarography is rarely used in mycotoxin analysis. Kruglyak et al.[568] found no significant differences between d.c. polarographic and biological data for the assay of trichothecin in fermentation broth. The studied concentration range is given as 7×10^{-6} to 7×10^{-7} *M*.



D.p.p. can provide an accurate and sensitive method[567] for the determination of aflatoxin B_1, B_2, G_1, and G_2 in various foodstuffs. Tested food matrixes were rice, pelletised feed, milk, and corn. The limit of detection for the differential pulse polarographic method following chromatographic separation was found to be 0.15 μg $m\ell^{-1}$ for a 5-mℓ fraction of eluent. This permits the determination of 1 to 2 μg g^{-1} of the aflatoxin in the original material when 50 g of material was taken for analysis.

3. Combination of HPLC and Electrometric Detection

Direct simultaneous determination of isomeric chloroanilines based on their oxidation on a glassy carbon electrode in metabolic products of chlorinated phenylamides used as herbicides is not possible due to a small difference in their oxidation potentials. HPLC with amperometric detection enables determination of 2- and 4-chloroaniline down to 2 ng and 3-chloroaniline down to 1 ng for a 20-μℓ injection on the chromatographic column.[569]

Electrochemical detection in HPLC was also applied to residue analysis of the fungicide dithianon (2,3-dicyano 1,4-dihydro-1,4-dithioanthraquinone) in fruits, with a glassy carbon working electrode.[570]

A further recent example is the use of HPLC combined with electrochemical wall-jet cell detector for the electroanalytical estimation of 11 herbicides (carbamates: Propham, Chlor-

propham; ureas: Monolinuron, Metabromuron, Linuron, Chlorbromuron, Femuron, Chlortoluron, Fluometuron, Diuron, Chloroxuron).[570a]

XIII. PHARMACEUTICALS

Polarography was applied to problems of pharmaceutical and biological analysis early in the development of the method.[222,571-575] Such early successful application is best explained by the fact that in drug analysis the samples are well defined, even when they are rather complicated mixtures of an approximately known composition.[104,576]

The early interest was sustained in the 1950s,[13] but that was followed by a period of limited number of applications in the 1960s, particularly in the West and North America.[249] In the 1970s, a renewal of interest occurred, generated by (1) the development and availability of the new generation of polarographic equipment offering the pulse mode with increased resolving power and increased sensitivity; (2) the considerable growth of understanding of electrode processes involving compounds of pharmaceutical interest; and (3) application of waves due to oxidation processes,[577] thus making the technique applicable to a wider range of pharmaceutical preparations.

The regained interest in application of polarography and voltammetry in pharmacy extended also to pharmacology and medicinal chemistry. The growth of interest has also gained in related fields such as pure and applied biochemistry and biotechnology, clinical chemistry, medical research, toxicology, and industrial hygiene. Several modern books[105,578-582a] and review articles[104,137,251,252,344,576,583-596] provide comprehensive discussions of the electrochemistry of drugs and their applications. According to Fogg,[597] the answer to the question — "Voltammetry, is it worth considering?" — is an emphatic "yes", for the determination of drugs in preparations and formulations and in biological materials.

A remarkable advantage of polarographic methods in the analysis of formulations such as injections, tablets, dragées, oily solutions, ointments, creams, etc. is that excipients do not interfere to such a great extent as they do in other methods. Dragées, e.g., can often be analyzed in presence of unsoluble tablet materials.

The acceptance of the significance of polarography and voltammetry is featured by the fact that the USP XX quotes 16 drugs and formulations assayed by polarography. The future trends are assumed[592] to result in: (1) a vigorous development in the area of detector design and applications of studies of HPLC electrometric detection, which necessitates a good knowledge of the electrochemistry of the compounds and systems studied; (2) stripping voltammetry will encompass a wider range of organic and organometallic molecules; (3) electrochemical methods will have to provide more information on the identity of unknown molecules giving rise to currents at a particular working electrode; and (4) pattern recognition, where peak currents, potentials, and signal width of the electroactive molecule will be of importance. These approaches could be complemented by the use of chemically modified working electrodes designed to react with a particular reactional group in the molecule under study.[592]

Extensive discussion of recently published papers on polarography and voltammetry of drugs and pharmaceutically relevant substances is beyond the scope of this article. Typical examples taken from the author's laboratory are summarized in Figure 40.

Selected, less common applications in practical drug analysis will be discussed in the next two sections.

A. Direct and Indirect Assay of Drugs via Metal Complexes

The removal of excessive amounts of iron from the body — whether stored as a result of pathological conditions or from acute poisoning — can be achieved with biologically derived Desferal® (a polymer of three molecules of trihydroxamic acids) better than with chelating agents such as EDTA which tend also to remove other essential metals, such as

Field of Application		Discussed in Section
RESEARCH/PHARMACO KINETICS	- RESORPTION /TOXICITY STUDIES of DRUGS : determination of NO_2-CGP-X in blood/urine of test-animals	II.4.4.3
PRODUCTION	- QUALITY CONTROL of INTERMEDIATES	III.5.2.
	- CONTENT of RAW PRODUCTS	III.3.2.
PHARMA FORMULATIONS	- ASSAY of PURE DRUGS	II.1.4./3.1.1.
	- QUALITY CONTROL of EXCIPIENTS	II.3.2.
	- DETERMINATION of ADDITIVES (in excipients and formulated forms)	II.4.4.3.
	- DETERMINATION of ACTIVE COMPOUND in FORMULATED DOSAGE FORMS	II.1.4./3.1.2.
	- DETECTION of BYPRODUCTS (impurities,degradation products) in ACTIVE COMPOUND/FORMULATED DOSAGE FORM	II.4.4.1. II.1.2.

FIGURE 40. Applications of polarography and voltammetry to drug analysis.

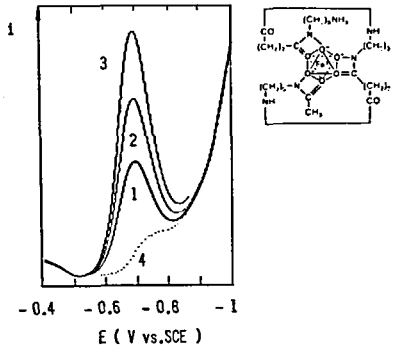


FIGURE 41. Differential pulse polarograms of Desferal® and ferrioxamin. Urine sample (1) prior to complexation; (2) after complexation; (3) + 18.3 μg ferrioxamin $m\ell^{-1}$ urine; (4) blank urine.

copper and magnesium. Desferal® removes iron from various iron-containing proteins in the body (e.g., ferritin, hemosiderin), but not from hemoglobin or iron-containing enzymes.[598] Desferal® has little or no affinity for calcium, cobalt, or other metals, but forms with iron the water-soluble chelate ferrioxamin which yields a well-defined, reversible reduction wave[599,600] (Figure 41). In most patients, the bulk of iron chelated by Desferal® appears in the urine.[598] The advantage of polarographic assay is that both the formed ferrioxamin and the nonchelated drug can be determined in the same urine sample (Figure 41), the latter after complexation in the urine containing supporting electrolyte.[115] A differentiation of the different known biological metabolites is, however, not possible by this procedure.

The same indirect technique was used for the determination of desferricrocin — a parent compound of Desferal® — in fermentation broth. Polarography was used mainly to control desferricrocin formation in function of the fermentation time.[115]

A fast, reliable analytical method to optimize the yields in everninomicin in the course of laboratory fermentation is based on d.p.p. assay.[601] Because of its rapidity, polarography was proposed for the determination of trichotecin in fermentation broth.[568]

Clark et al.[602] recently studied the polarographic behavior of copper complexes of pilocarpine and some related imidazoles. The alkaloids pilocarpine and brucine are electrochemically inactive. The catalytic wave at pH 8 reported for high concentrations of pilocarpine at −1.95 V vs. SCE[603] was found to be of little use. They observed that, while the wave

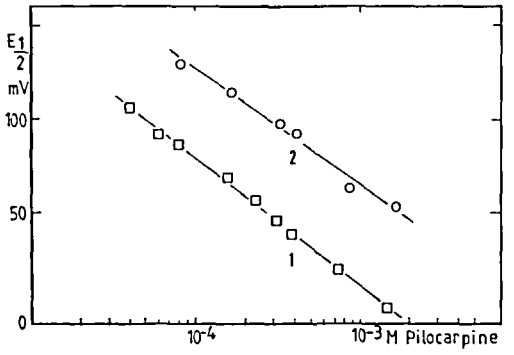


FIGURE 42. Determination of pilocarpine in copper citrate medium according to Clark et al.[602] Calibration graph (1) data given by Clark et al.; (2) data found in the author's laboratory.[115]

heights are independent of the pilocarpine concentration in a copper-citrate system, the half-wave potentials of copper(II)-copper(I) are controlled by the concentration of the second ligand, when this has an imidazole nucleus. The effect depends on copper(II) ions being complexed by citrate, and copper(I) ions by the ligand of interest.

The first wave, measured by differential pulse polarography, was adopted as the basis of an analytical procedure for pilocarpine. For determination a calibration curve is used. Pilocarpine concentrations obtained from the calibrated shifts of the half-wave potentials ($E_{1/2}$) resulting from addition of 20 mm^3 of pilocarpine nitrate solutions to 2.5 cm^3 copper-citrate are given for samples of 10, 30, 70, and 100 mM pilocarpine. The error is within $\pm 10\%$ for the lowest concentration and $\pm 2\%$ for the highest. Figure 42 shows the calibration graph constructed with literature values[602] as compared to our own measurements.[115] The technique may be applicable to all ligands capable of forming copper(I) complexes in solution.

The labile copper(II) chelate formed with bromazepam gives rise to a catalytic phenomena at the hanging mercury drop electrode which can be employed for the differential pulse polargraphic determination of bromazepam in the concentration range from 10^{-5} to $10^{-9}M$ in bromazepam and 10^{-4} M in copper(II) ions.[604] A linear peak height concentration dependence was found in the concentration range mentioned. This method is superior to an earlier one which was based on differential pulse anodic stripping voltammetry of the free copper(II) ions remaining after complexation of an excess (5×10^{-7} M) of copper(II) ions with broamazepam. The calibration curve found obeyed a sigmoidal relationship, with limited linearity in the concentration range from 1.5 to 4×10^{-7} M bromazepam,[605] whereas in the aforementioned procedure,[604] a plot of peak height (reduction of $> C = N-$) on the concentration of bromazepam was found to be linear in the concentration range from 10^{-5} to 10^{-9} M.

A cathodic stripping method for the assay of ultratraces of different penicillins (benzylpenicillin, ampicilin, phenoxy-methylpenicillin, and cloxacilin) is based on metal complex formation.[288,289] The accumulation is performed at a hanging mercury drop electrode at -0.1 V vs. SCE in an acetate buffer, pH 4.6, consisting of 0.05 M sodium acetate and 0.05 M acetic acid in triple-distilled water containing an excess of copper(II).[289] Solutions of copper(II) of 10^{-5} to 10^{-6} M are usually employed. When very low penicilloic acid levels are to be measured, a copper(II) level of 10^{-7} to 10^{-6} M is preferred. During accumulation a copper complex of penicillamine is formed which is subsequently reduced at about -0.4 V vs. SCE in the stripping step. The detection limits given are 1×10^{-9} M after 1 min accumulation time and 1×10^{-10} M for 10 min accumulation time. A linear calibration graph was found for the concentration range from 2×10^{-9} to 1×10^{-7} M penicilloate solution in presence of 2×10^{-6} M copper(II), using the differential pulse mode and an

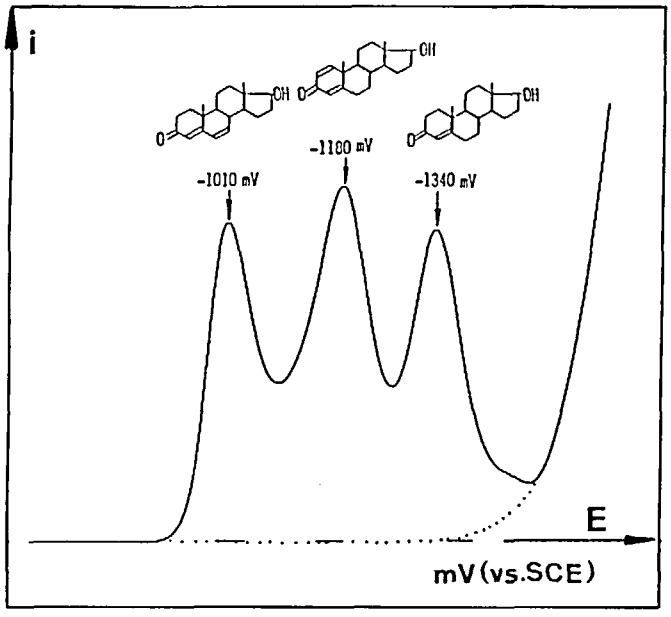


FIGURE 43. Dependence of the differential pulse polarographic peak potential (E_p) on the position of the conjugated system in Britton Robinson buffer pH 4 with 50% ethanol.[115]

accumulation time of 1 min. At concentrations above 10^{-7} *M*, the slope of the dependence of peak height vs. concentration slowly decreases. When the linear sweep mode is applied, either the peak height or the peak area may be evaluated. As it is the sulfur-containing five-membered ring connected to the hydrolyzed β-lactam ring which reacts with the mercury, it is probable that other penicilloates will be suitable for cathodic stripping.

B. Polarography of Steroids: Determination of Epimers in Production and Quality Control

The electrochemistry[606] and polarography of steroids[122,607-614] have been well documented. In the past 4 to 5 years a strong interest has been shown in the polarographic behavior of pure substances and the polarographic assay of formulated dosage forms.

A general discussion of the polarography of steroids is beyond the scope of this article; the reader is referred to the original literature and also to recent studies on the polarographic analysis of corticosteroids.[615-621] The most common naturally occurring steroids which can be determined by polarographic methods are those containing a keto group, e.g., 3-keto-steroids. The half-wave potential varies with the nature of the conjugated system (Figure 43).

It is generally true that conjugation of the double or triple bond of the electroactive group with a multiple bond or with an aromatic ring facilitates the reduction. Furthermore, in compounds containing a system of conjugated multiple bonds, the whole system of conjugated bonds represents a single grouping.[195]

However, not all reductions are facilitated by the presence of double bonds in the vicinity of the electroactive group. A double bond in β-position of the allyl type facilitates the reduction of the carbon-halogen bond, compared with the corresponding allylhalogenide; however, a double bond in the α-position in compounds of the vinyl type makes the reduction of the carbon-halogen bond more difficult:[195]

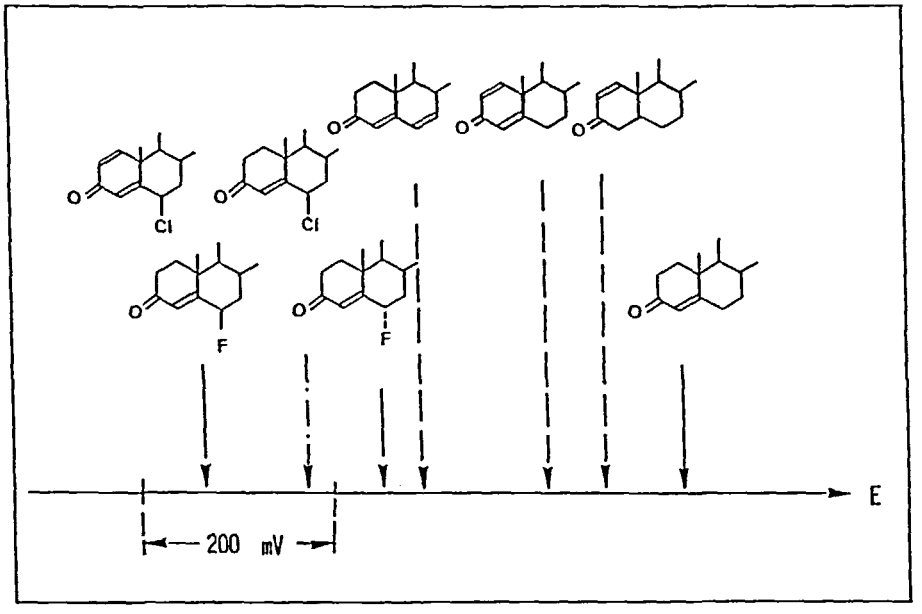


FIGURE 44. Dependence of the half-wave potential ($E_{1/2}$) on the structure of 3-keto-steroids. (From Hrdý, O., Coll. Czechoslov. *Chem. Commun.*, 27, 2447, 1962; Hrdý, O., *Abh. Deut. Akad. Wiss.*, Berlin, 1964, 109. With permission.)

The half-wave potentials of halogeno-keto-steroids also vary with the steric position of the electronegative substituents. The equatorial halogen isomer is always more difficult to reduce than the axial form. The difference increases in the sequence Br < Cl < F (Figure 44).

The introduction of fluorine in certain positions on the ring system with given stereochemistry greatly intensifies the biological activity, so that the therapeutic dosage can be lowered and side effects decreased proportionally. In some cases, polarography enables determination of the biologically active epimer in presence of the inactive ones. Nevertheless, whereas for 6α- and 6β-fluorine derivatives the difference between the half-wave potentials is considerable, for 6α- and 6β-methyl it is rather small (Figure 45).

Further information on the role of steric effects in the reduction of steroids can be found in References 608, 609, and 612 to 614. Various modes of polarography are used for the determination of α- and β-fluorenone in the production control of this intermediate[251] (Figure 46).

D.p.p. can determine 0.3% of the β-fluorenone in the α-product. The peak currents are a linear function of the concentration of the steroid in the range between 0.3 to 2% of β-fluorenone.

For the determination of α-fluorenone in the raw product, sampled d.c. polarography was used. Relative standard deviations from 0.7 to 1.3% for α-fluorenone contents from 58 to 99% are found.[251]

The differential pulse polarographic assay proved to be very useful for rapid assessment of the quality of commercial products, as shown by Figure 47. The competition product (b) exhibits a large additional reduction wave due to a byproduct (impurity).[251]

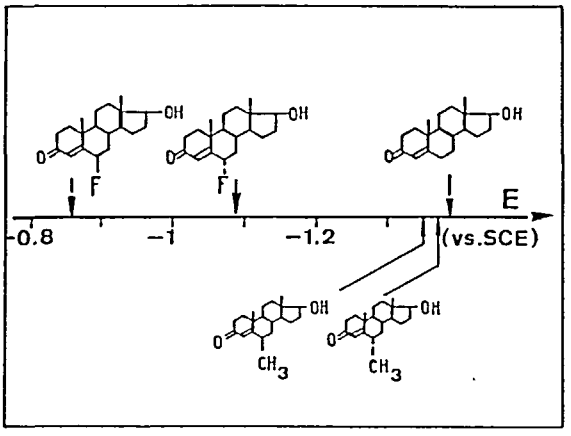


FIGURE 45. Half-wave potentials ($E_{1/2}$) of epimeric F- and methyl-keto-steroids in Britton Robinson buffer pH 6 with 50% ethanol.[115]

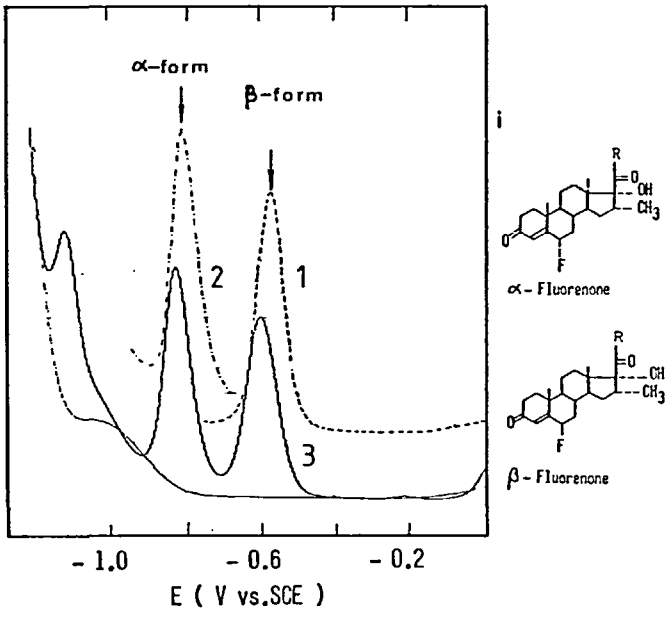


FIGURE 46. Differential pulse polarograms of β- (axial) and α- (equatorial) fluorenone in Britton Robinson buffer pH 1.9 with 30% DMF. D.p.p.: drop time 1 sec; scan rate 5 mV sec^{-1}; pulse amplitude −50 mV. (1) axial; (2) equatorial form; (3) mixture 1:1. (From Bersier, P. M., *J. Pharm. Biomed. Anal.*, 1, 475, 1983. With permission.)

XIV. CONCLUSIONS

This article has tried to show the diverse ways in which polarography and voltammetry can be used in determination of organic compounds and it is hoped that the examples given illustrate the point that laboratories working in the organic field should consider the benefits these techniques can offer.

Polarography and voltammetry are not general-purpose methods: they have various disadvantages similar to other instrumental methods and therefore a critical assessment of the scope of their application should be made in each case.

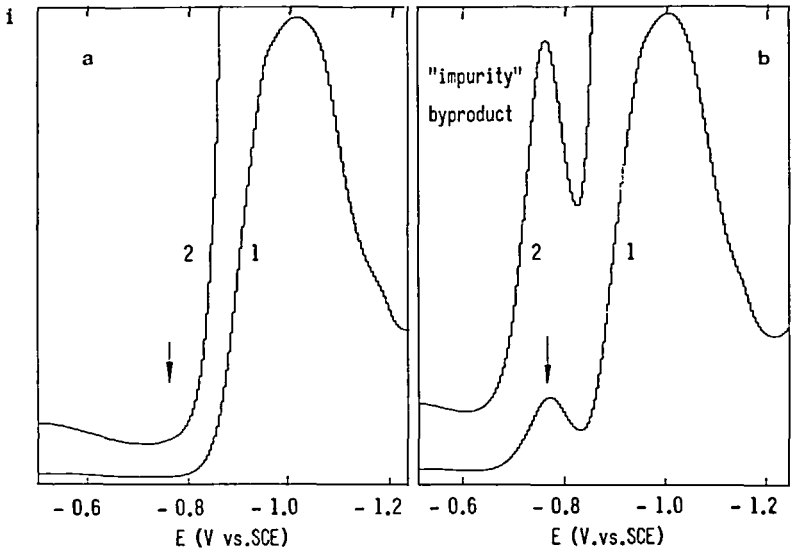


FIGURE 47. Comparison of the differential pulse polarograms of (a) own and (b) competition product. Full-scale sensitivity curve (1) = 5 μA; curve (2) = 1 μA. (From Bersier, P. M., *J. Pharm. Biomed. Anal.*, 1, 475, 1983. With permission.)

As emphasized by Professor Zuman in reference to organic systems and Professor Nürnberg to inorganic systems, the relationships between polarography and voltammetry and other instrumental techniques in organic and inorganic applications should be complementary rather than competitive.

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