CHAPTER 15

Coulometric Methods and Chronopotentiometry

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15.1 INTRODUCTION

A. ELECTROLYSIS[1]

Electrolysis, the passage of a direct current between a metallic conductor (*electrode*) and an electrolytic solution, is the basis for the instrumental techniques of *coulometry* and *chronopotentiometry*. It causes a chemical reaction to take place at the electrode surface by the following steps: (1) mass transfer of the electroactive species to the electrode surface under a concentration gradient, (2) the transfer of one or more electrons to the electroactive species, and (3) the removal of the products.

B. VOLTAMMETRY[2]

Electroactive compounds will give steady-state current-potential curves such as those shown in Fig. 15.1, when the electrolysis current is plotted against the potential of the working electrode (vs. a reference electrode such as a calomel electrode). Curve *a* is obtained during the electrolysis of the solvent containing electrolyte alone, while curve *b* is obtained in the presence of an electroactive compound in the electrolytic solution. The plateau in curve *b* is the *limiting* current. The increase in current over the background of the plateau region is called the "diffusion current" of the electroactive species. The potential at which the electrolysis current is equal to half the diffusion current is called the "half-wave potential" ($E_{1/2}$) of the electroactive species.

C. CURRENT-CONCENTRATION RELATIONSHIP

Controlled potential coulometry involves the complete electrolysis of the electroactive species. The current during the electrolysis is always *equal* to the diffusion current of the electroactive species. *Constant current coulometry* involves the complete titration of a compound (whose presence or lack of electroactivity is irrelevant) by a titrant which is electrochemically generated by a current *less* than the diffusion current of the electroactive titrant precursor. *Chronopotentiometry* involves limited electrolysis under conditions

of constant current *in excess* of the value of the diffusion current of the electroactive species.

D. HISTORICAL

1. Constant Current Coulometry

Although coulometry was first used by Grower[3] in 1917, as an analytical method for checking the quality of tinned copper wire, the term was only

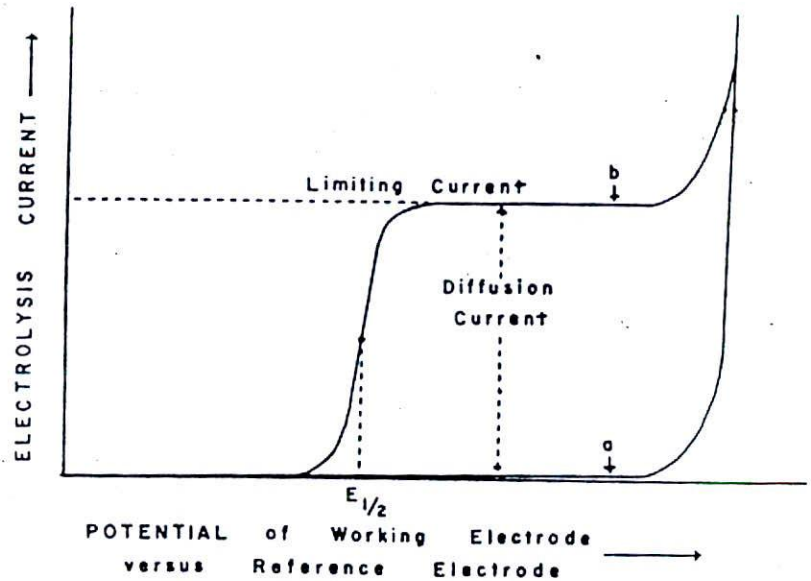

FIGURE 15.1: Curve a: voltammetric curve for solvent with supporting electrolyte; curve b: voltammetric curve for electroactive species in solvent with supporting electrolyte.

introduced in 1938 by Szebelledy and Somogyi,[4] who pioneered in constant current coulometry as a substitute for classical volumetric methods. Swift[5] and others[6] have further developed the technique by using modern end-point detection methods.

2. Controlled Potential Coulometry

Controlled potential coulometry was initiated by Hickling[7] in 1942, and further elaborated by Lingane[8] in 1945.

3. Chronopotentiometry

Gierst and Juliard[9] in 1951 recognized the analytical potentialities of chronopotentiometry, which Sand[10] had first studied in 1901.

E. COULOMETRY[11,12,13]

Coulometry is essentially a titrimetric (volumetric) technique, where electrons are used as the titrant. The three components of a volumetric setup (Fig. 15.2): (1) the titrant and its corresponding titrant storage vessel,

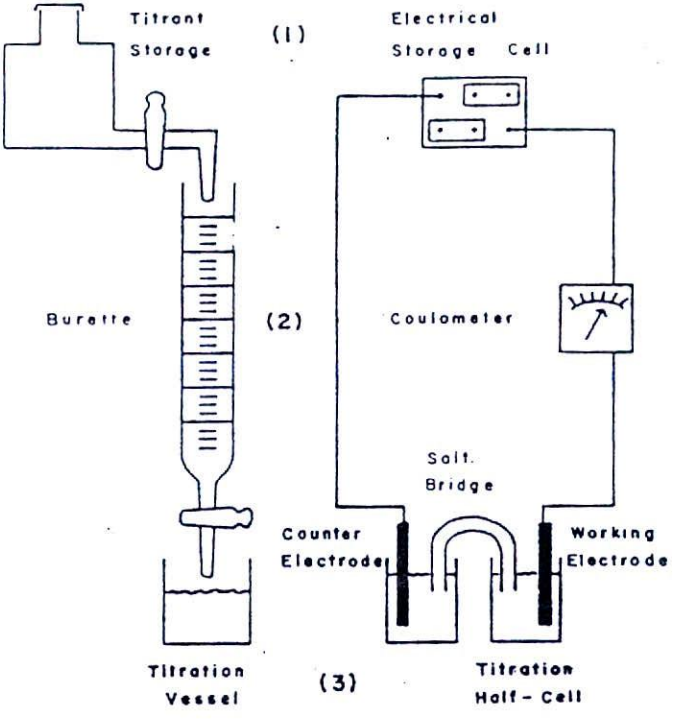

FIGURE 15.2: Comparison of volumetric and coulometric setups.

(2) the calibrated burette, and (3) the titration vessel are replaced by (1) an electrical storage cell, (2) a coulometer (a counter of coulombs), and (3) an electrical half-cell containing a suitable working electrode to introduce the electrons into the solution. An end-point detector which is necessary to feed a monitoring signal into a control device to turn off the burette in titrimetry is also necessary to turn off the coulometer in coulometry.

Coulometry can be divided into two basic types, the *direct* (or primary)

and the *indirect* (or secondary). Primary coulometry is limited to the direct titration of electroactive substances with electrons. These all fall into the redox type of titration category as indicated by Eq. (15.1) and (15.2):

$$\text{reduced species} - ne\ (\text{titrant}) \rightarrow \text{oxidized species} \tag{15.1}$$

$$\text{oxidized species} + ne\ (\text{titrant}) \rightarrow \text{reduced species} \tag{15.2}$$

Secondary coulometry involves the indirect use of the electron titrant to electrogenerate chemical titrants, as indicated by Eq. (15.3) and (15.4):

$$\text{reduced species} - ne \rightarrow \text{oxidized species (titrant)} \tag{15.3}$$

$$\text{oxidized species} + ne \rightarrow \text{reduced species (titrant)} \tag{15.4}$$

Secondary coulometry is not limited to substances which are electroactive. It can be used as a direct substitute for the usual titrimetric procedures involving (1) *redox*, (2) *acid-base*, (3) *complexation*, and (4) *precipitation* titrations as long as the titrant can be electrochemically generated.

In coulometry, the quantity of material being titrated is determined by the quantity of electricity (coulombs) required to react with it. Thus it is obvious that the success of this procedure depends on the use of a suitable, precise, and accurate coulometer.

F. FARADAY'S LAW[14]

Coulometry is based on Faraday's law of electrolysis, which states that the extent of the chemical reaction that occurs as a result of electrolysis is directly proportional to the amount of electricity that is passed. The proportionality constant is the Faraday F, which has the value 96,487 coulombs/equivalent. Faraday's law may be expressed by Eq. (15.5), where w is the weight in grams of the species

$$\int_0^t i\,dt = Q = F(w/M)(n) \tag{15.5}$$

that is consumed during the electrolysis, M is its molecular weight, n is the number of electrons involved in the reaction, and Q is the number of coulombs used.

G. STOICHIOMETRY

As with all titrimetric procedures, quantitative stoichiometry is desired; this is obviously equated to *100% current efficiency*. To achieve this, there should be no side reactions involving either (1) the solvent, (2) the electrode, (3) the substances which are not consumed in the electrode process (supporting electrolyte and dissolved oxygen), or (4) the products of the electrolysis.

15.2 CONTROLLED POTENTIAL COULOMETRY[11]

A. CURRENT-POTENTIAL-TIME RELATIONSHIP

1. One Component

Primary coulometry (*potentiostatic coulometry*) is carried out by *controlling the potential* of the working electrode to limit the half-cell reaction to the one being studied. Thus the potential-time relationship is invariant. The current, however, is limited by the rate of diffusion of the electroactive substance from the bulk of the solution to the electrode surface. This results in the electrolysis current i being proportional to the bulk concentration C of the substance as shown in Eq. (15.6).

$$i = kC \tag{15.6}$$

Since the material is consumed by a first-order kinetic rate, the instantaneous bulk concentration and consequently the instantaneous electrolysis current (i) decreases exponentially as shown in Eq. (15.7), where i_0 is the initial electrolysis current.[15]

$$i = i_0 e^{-k't} \tag{15.7}$$

The rate constant k', in reciprocal seconds, can be calculated from Eq. (15.8):

$$k' = DA/v\delta \tag{15.8}$$

where D is the diffusion coefficient of the electroactive species in square centimeters per second, A is the electrode area in square centimeters, v is the total volume of the solution in cubic centimeters, and δ is the thickness of the diffusion layer in centimeters. The diffusion layer is pictured as a thin layer of solution which remains stationary about the electrode surface even though the bulk of the solution is in motion: diffusion into and out of this layer occurs during electrolysis. The time of electrolysis is affected by factors which influence diffusion such as stirring rate and temperature.

2. Two Components

A mixture of compounds having sufficiently different half-wave potentials (0.1 V or more) as shown in Fig. 15.3 may be run. Only the most easily reduced (or oxidized) substance a can be selectively reduced. If the potential E_2 is great enough to reduce (or oxidize) substance b, all species (such as substance a) that are more easily reduced (or oxidized) will be electrolyzed simultaneously with substance b. If it is desired to reduce (or oxidize) only substance b, which is the more difficult one, it will be necessary first to reduce substance a completely at the proper potential (E_1).

B. END-POINT DETECTOR

Controlled potential coulometry has a built-in end-point indicator, i.e., the electrolysis current. The electrolysis is carried out until a predetermined current level is reached with the current indicator or recorder serving as the end-point detector.

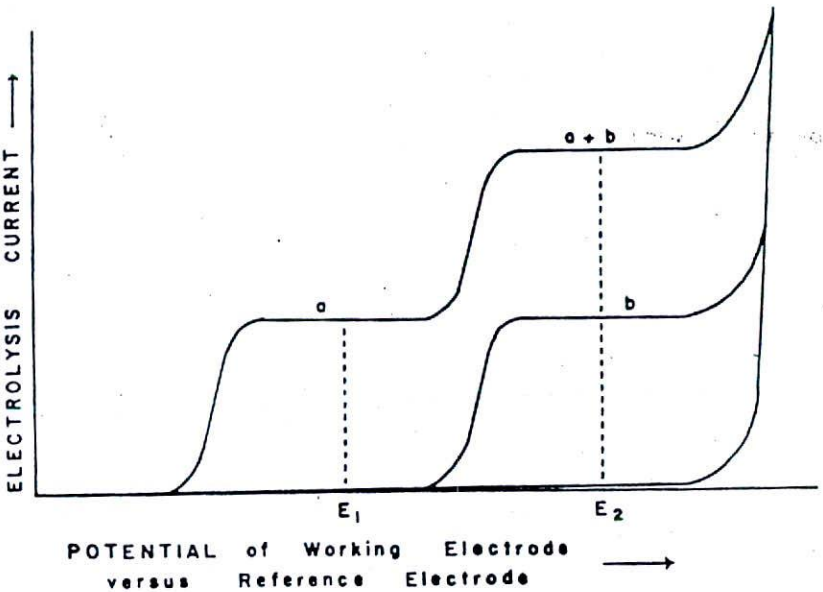

FIGURE 15.3: Voltammetric curves for (1) solvent with supporting electrolyte; (2) substance *b* in solvent with supporting electrolyte; and (3) substances *a* and *b* in solvent with supporting electrolyte.

C. CIRCUIT

A simplified circuit for controlled potential coulometry is shown in Fig. 15.4. It consists of the following items:

1. Power Supply

A direct current power supply which can maintain the working potential at a constant level is used in controlled potential coulometry. In Fig. 15.4 a battery (E_B) and potentiometer (R_1) are used. Point *c* is varied either manually,[11,16] electromechanically,[17] or electronically[18] to maintain a constant

potential E_c on the working electrode, as indicated by a high-input impedance electronic voltmeter V.

2. Electrolysis Vessel

A three-electrode electrolysis vessel (Fig. 15.5) is used for the titration. It contains (a) a *working electrode* where the titration is taking place, (b) a *reference electrode* (usually a calomel electrode), which is used to determine the potential of the working electrode by comparison, and (c) a *counter electrode* (sometimes called an *auxiliary electrode*) to complete the electrical circuit from the controlled dc power supply. Optimum cell design implies a

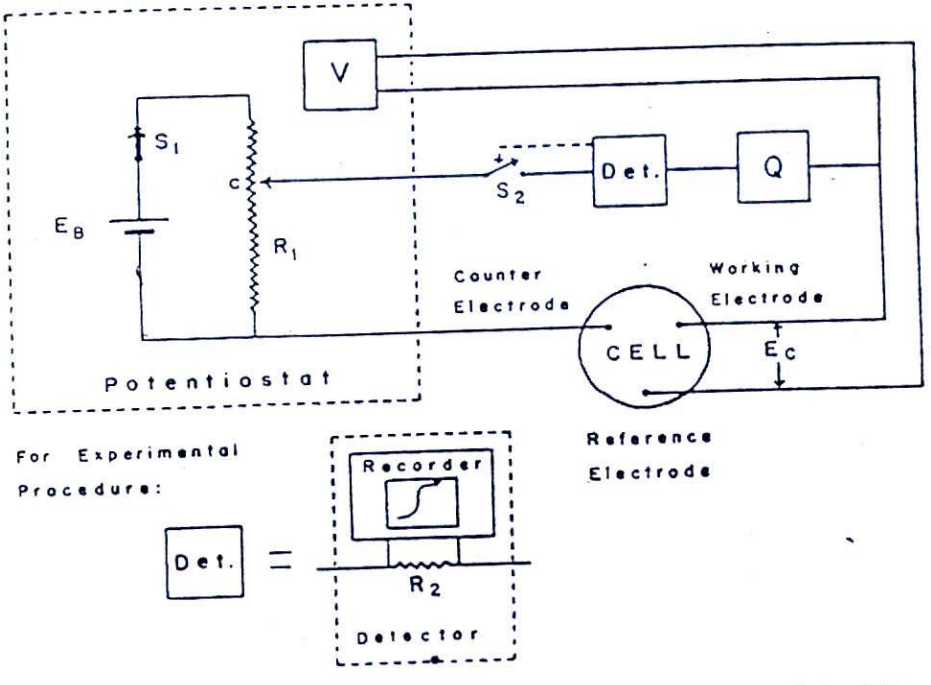

FIGURE 15.4: A simplified circuit for controlled potential coulometry where E_B is a 6-V storage battery, R_1 is a 50-Ω, 2-W, 10-turn potentiometer, R_2 is 0.100-Ω precision (±0.05%) resistor, S_1 and S_2 are SPST switches, Q is a coulometer, V is a high-input impedance electronic voltmeter such as a pH meter, and *Det.* is the end-point detector.

large electrode area, small solution volume, and a high stirring rate. Each half-cell is usually separated from the other half-cells by porous diaphragms (with an agar plug) or salt bridges to prevent the contamination of the individual compartments with electrolysis products.

3. Coulometer

The number of coulombs, Q, used in the reaction is determined by Eq. (15.9) and can be calculated[19,20] directly by use of Eq. (15.10) or (15.11) if the rate constant, k', is known.

$$Q = \int_0^t i\,dt \tag{15.9}$$

$$Q = \int_0^t i_0 e^{-k't}\,dt = (i_0/k')(1 - e^{-k't}) \tag{15.10}$$

$$Q = \int_0^\infty i_0 e^{-k't}\,dt = i_0/k' \tag{15.11}$$

a. Graphical. The current-time curve may be integrated graphically. This may be done by (1) cutting out the current-time curve obtained from a

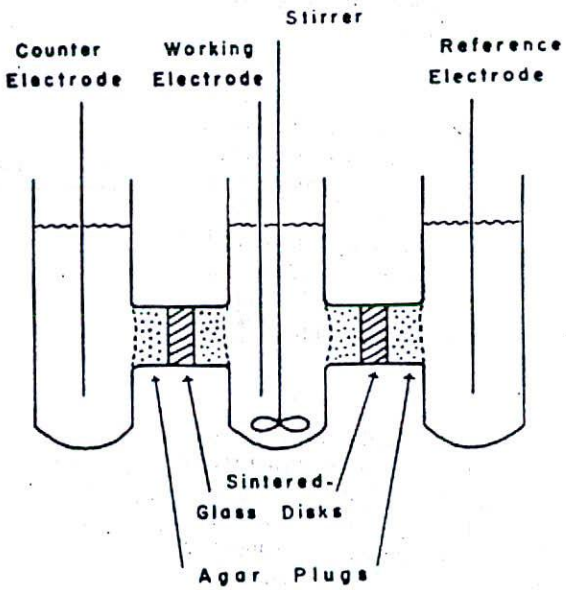

FIGURE 15.5: A three-electrode electrolysis vessel for controlled potential coulometry and chronopotentiometry.

strip chart recorder, and comparing its weight with a square of the same paper of known area by (2) using a planimeter or (3) with a ball-and-disk integrator[11,21] attached to the recorder.

b. Chemical. Chemical coulometers depend on the electrochemical preparation of a compound and its subsequent quantitative determination by

any of the following chemical methods: (1) gravimetric,[22–24] (2) titrimetric,[23] (3) gasometric,[8,25] and (4) colorimetric.[26]

c. Electromechanical. Current-time integrators are available which make use of: (1) low inertia integrating motors,[27–30] (2) analog (*operational amplifier*) integrators,[18,31] and (3) current (via voltage) to frequency converter with a frequency counter.[32,33]

D. EXPERIMENTAL CONDITIONS

1. Electrode

a. Material. The most widely used electrode materials are mercury and platinum. Mercury is satisfactory mainly as a cathode and platinum is used as either an anode or a cathode. Other electrodes such as boron carbide,[34] carbon black,[35] carbon paste,[36] gold,[37] and graphite[37,38] have been used to a limited extent.

b. Potential Range. Because of the overpotential of hydrogen on mercury (ca. 1.2 V), mercury can be used in basic solutions and nonaqueous solutions as a cathode at potentials as negative as −2.8 V vs. a saturated calomel electrode (SCE), while its use as an anode is limited to about +0.3 V (vs. SCE) because of anodic dissolution.

Platinum, however, does not have an appreciable overpotential for hydrogen, thus its potential as a cathode in basic solutions is limited to about −1.1 V (vs. SCE). The inertness of platinum enables it to be used as an anode to about +1.1 V vs. SCE in aqueous solutions and higher potentials (ca. +2.0 V vs. SCE) in acetonitrile.[39,40]

2. Solvent

a. Electrolyte. A highly ionizable soluble salt (in concentrations 50–100 times the electroactive species being studied), the supporting electrolyte, is used to conduct the electricity in the solvent. It should not be involved in electrode reactions. To obtain the largest potential range possible for cathodic half-cells, difficultly reduced cation salts such as quaternary ammonium salts may be used and for anodic half-cells, difficultly oxidized anion salts such as perchlorates may be used.

b. pH. The pH of the solution affects both the electroactive species and the background current. The former effect occurs only with material whose redox potential is pH sensitive. For these the $E_{\frac{1}{2}}$ is smaller in acidic media for cathodic reactions and larger for anodic reactions. The reverse holds true in basic media. The background current in aqueous solutions may be due to the following reactions

$$H^+ + e^- \rightarrow \tfrac{1}{2}H_2 \qquad (15.12)$$

$$H_2O - 2e^- \rightarrow \tfrac{1}{2}O_2 + 2H^+ \qquad (15.13)$$

causing the production of hydrogen at the cathode and oxygen at the anode. These processes impose an upper limit on the potentials that the working electrode can assume since they obscure other electrolyses. Reactions (15.12) and (15.13) are pH dependent, the discharge of hydrogen ions occurs more easily in acidic solutions, while the oxidation of water occurs more easily in basic solutions.

c. Oxygen. If oxygen is reduced at a lower potential than the electrode reaction of interest, it must be removed to insure 100% current efficiency. This is usually done by deoxygenating with nitrogen. Oxygen does not normally interfere in anodic half-cell reactions.

d. Temperature. To decrease the electrolysis time, the electrolysis cell may be operated at an elevated temperature. This results from the fact that the diffusion coefficient of the electroactive species increases approximately 2%/deg.

e. Mixing. A high rate of stirring minimizes the diffusion layer and thus reduces the electrolysis time.

3. Potential

The potential of the working electrode is chosen to (a) give the desired half-cell reaction, (b) minimize background (or *blank*) current, and (c) give the desired separation from other electroactive materials that may be present.

4. End Point

The electrolysis may be discontinued when the ratio i/i_0 (equal to the ratio of the concentration C_t remaining unreacted at time t to the initial concentration C_0) decreases to a value corresponding to the degree of completion desired. For 99.9% completion the electrolysis must be terminated at 0.1% of the initial current. This termination current must also be at least as large as the background current.

5. Current Range

Electrolysis currents having magnitudes from 10 μA to 100 mA are adequate for controlled potential coulometry.

6. Concentration Range

Controlled potential coulometry has been successfully used for concentrations as high as 2×10^{-3} M and for concentrations as low as 5×10^{-8} M.[31,41]

7. Time

The usual range of times required for a complete controlled potential coulometry run is 10 to 60 min.

E. ADVANTAGES AND LIMITATIONS

Controlled potential coulometry offers a significant advantage over voltammetry in the precision which can be achieved in an analysis. However, this technique has limited use since voltammetry and polarography usually can be used for the same type of determination more rapidly, easily, and with simpler equipment.

1. Accuracy

The accuracy of controlled potential coulometry is only limited by the inability to maintain 100% current efficiency because of background current. Meites and Moros[42] have divided the background current into five components: (a) charging current, (b) impurity faradaic current, (c) continuous faradaic current, (d) kinetic background current, and (e) induced background current. The simplest way to minimize background-current errors is to utilize a relatively large quantity of the electroactive species, thereby making insignificant the contribution of the background current to the total Q.

2. Precision

The precision obtained in controlled potential coulometry is limited by the reproducibility of the coulometer used and is normally of the order of 0.3 to 1%.

F. PHARMACEUTICAL APPLICATIONS

Those compounds which are reducible or oxidizable by polarography or voltammetry (the study of currents when the current-voltage characteristics depend on the electrode reaction rate), and which have well-defined diffusion controlled waves can be run. Organic functional groups which are normally reducible are: (1) carbon-carbon double bonds when conjugated with another unsaturated group, (2) the carbonyl group in ketones and aldehydes, (3) nitro and related nitrogen compounds, (4) halogens, and (5) disulfides and peroxides. The typical oxidizable groups are aromatic amines and phenols. For more details see Chapter 16, on polarography.

Controlled potential coulometry has been reported for copper,[43] iron,[31] lead,[44] oxygen,[45–47] sodium,[48] tin,[44,49] anthraquinone,[50] ascorbic acid,[16] chlorpromazine,[51] hydrogen peroxide,[52] organic halogen compounds,[53] organic nitro compounds,[53–55] N-substituted phenothiazines,[56] phenylmercuric ion,[57] and water.[58]

Although very few pharmaceutical compounds have been studied,[59] it should be applicable to: (1) unsaturated carbonyl compounds such as corticosteroids (cortisone, hydrocortisone, prednisolone, and prednisone) and some antibiotics (chlortetracycline, griseofulvin, oxytetracycline, and tetracycline); (2) iodine compounds such as iodinated X-ray contrast agents

(iodoalphionic acid and iopanoic acid) and iodochlorohydroxyquin; (3) nitro compounds such as chloramphenicol and nitrofurantoin; (4) chloro compounds such as chlorobutanol, chloroform, and trichlormethiazide; and (5) mercurial preservatives such as phenylmercuric acetate, chloride, and nitrate. In seeking optimum conditions one may make use of the wealth of voltammetric and polarographic information that is available.

15.3 CONSTANT CURRENT COULOMETRY[59,60]

Secondary (amperostatic) coulometry, which is frequently referred to as "coulometric titration" is carried out by *controlling the current* to the working electrode. The potential of the working electrode is controlled indirectly by maintaining the electrolysis current at a level where it can never be limited by the rate of diffusion of the electroactive substance. Thus the current is less than that for controlled potential electrolysis, as indicated by Eq. (15.14)

$$i < kC \tag{15.14}$$

A. CURRENT-POTENTIAL-TIME RELATIONSHIP

1. One and Two Components

The current and potential of the generating electrode in a constant current coulometric run are essentially invariant with time. Thus one cannot differentiate between the presence of one or two components from any knowledge of the current-potential-time relationship of the working electrode. However, the differentiation is possible if a suitable end-point detection method for differentiation is available.

B. END-POINT DETECTOR

The current cannot be used as an end-point indicator because it is constant throughout the electrolysis. Other end-point detection methods common in titrimetry are used. They may be divided into (1) optical and (2) electrometric methods. The former consists of (a) visual,[61] (b) photometric,[62] and (c) spectrophotometric[63,64]; and the latter consists of (a) potentiometric[65,66] and (b) amperometric[67] (an end-point device whereby the concentration of an electroactive substance is measured by the current which results from its reaction at an electrode). In the electrometric end-point detection methods, a second pair of electrodes is necessary.

C. CIRCUIT

A simplified circuit for constant current coulometry is shown in Fig. 15.6 and consists of the following:

1. Power Supply

A constant current generator usually referred to as an "amperostat" is used. The one displayed in Fig. 15.6 uses a high voltage battery (E_{B_1}) as the voltage source. A large resistance (compared with the electrolysis cell) R_1 is placed in series with the titration cell to limit the current to the desired

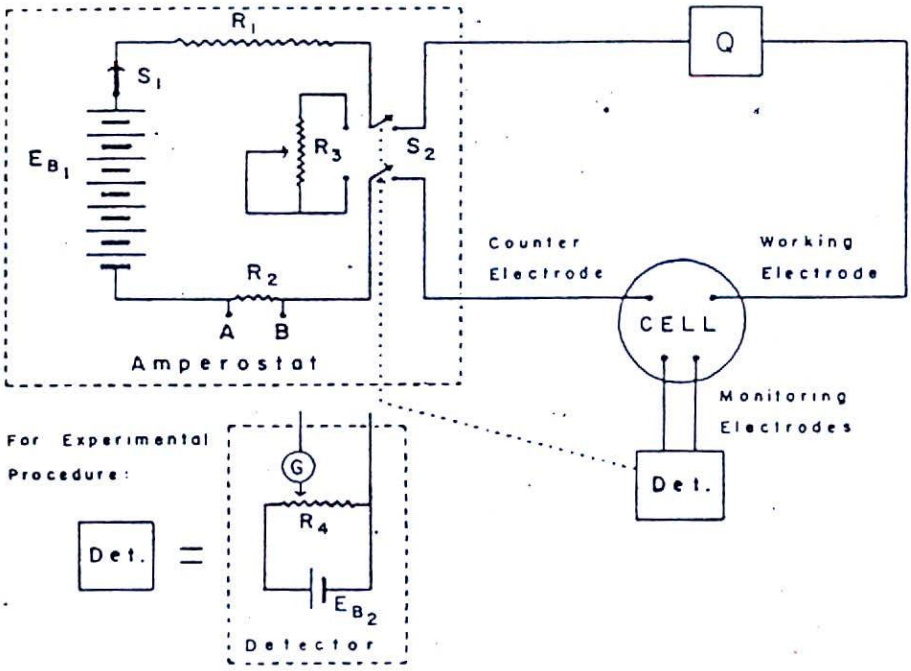

FIGURE 15.6: A simplified circuit for constant current coulometry where E_{B_1} is three 45-V dry-cell batteries, E_{B_2} is a 1.5-V dry cell, R_1 is a 7000-Ω, 10-W resistor, R_2 is a 50-Ω precision resistor (±0.05%), R_3 is a 100-Ω, 0.5-W rheostat, R_4 is a 1000-Ω, 10-turn potentiometer, G is a 20-μA meter, S_1 is an SPST switch, S_2 is a DPDT shorting switch, *Det.* is the end-point detector, and Q is the coulometer.

value and to make it independent of the effective electrolysis cell resistance. An amperostat can also be an electromechanical[68] or electronic[69–71] device.

2. Electrolysis Vessel

a. Internal Generation. In constant current coulometry, the electrolysis cell is simpler than in controlled potential coulometry because one half-cell (the reference electrode) is not needed. One should see that (1) the working electrode surface area is large enough for the intended electrolysis current

(current density ca. 0.5 mA/cm²/millinormal), (2) the contents of the cell are mixed rapidly and thoroughly so that the titrant is consumed as fast as possible, (3) the indicating system used responds quickly, and (4) when necessary, there are provisions for deoxygenation.

b. External Generation.[28,61,69,72,73] When conditions for obtaining a 100% current efficiency for the generation of the titrant are not compatible with the conditions for fast consumption of the titrant by the substance being titrated,[74] the titrant may be generated externally. Figure 15.7 illustrates

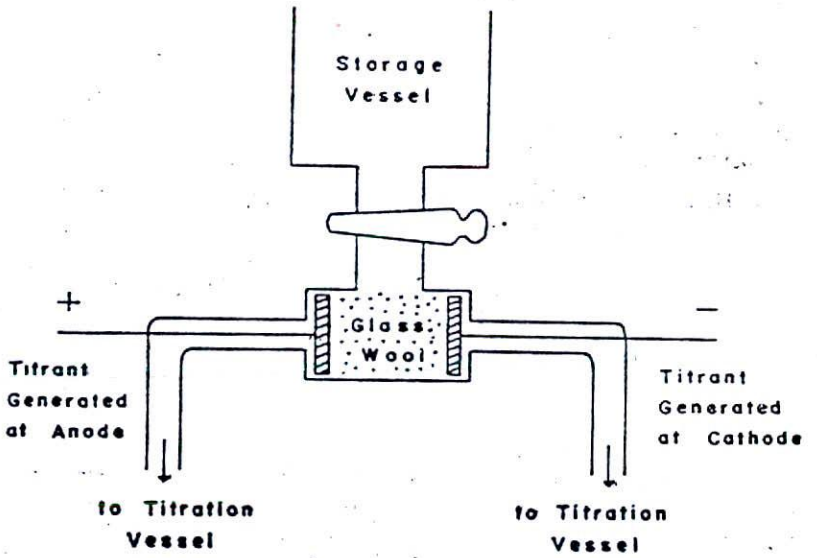

FIGURE 15.7: A constant current coulometric electrolysis vessel for the external generation of titrant.

an external electrolysis vessel. The titrating solvent containing the appropriate electrolyte flows through the electrolysis vessel and splits into two streams. One stream contains the product generated in the anodic compartment and the other, the product generated in the cathodic compartment. The appropriate stream flows into a standard volumetric titration flask.

3. Coulometer

A coulometer is used to integrate the constant current-time relationship shown in Eq. (15.15).

$$\int_0^{t'} i\,dt = i\int_0^{t'} dt = it \qquad (15.15)$$

In constant current coulometry, coulometers consist essentially of chronometers (timers). For most applications, synchronous electric timers operated by the commercial ac power frequency (60 Hz) are used.[66] However, for the greatest precision, electronic stop clocks with built-in precision electronic timers are used.[75,76]

D. EXPERIMENTAL CONDITIONS

1. Electrode

a. Material and Potential Range. The material and potential range are identical to those used for controlled potential coulometry.

2. Solvent

a. Electrolyte. In addition to carrying the current, the electrolyte is generally involved in the electrode reaction by being the electroactive chemical titrant precursor.

b. pH, Oxygen, and Temperature. These influences are identical to those in controlled potential coulometry.

c. Mixing. A high rate of mixing is necessary not to limit the indicator response by assisting in having the titrant react quickly with the substance to be titrated. If the titration reaction is limiting in spite of adequate mixing, *back titration* methods[77–81] must be used.

3. Potential

The potential is not directly controlled. However, the redox buffer resulting from the electroactive titrant precursor and the electrode reaction product usually stabilize the potential of the working electrode and prevent it from drifting.

4. End Point

A sharp change in voltage or current is normally used as an end point by most of the end point detectors.

5. Current Range

Electrolysis currents having magnitudes from 1 to 100 mA are adequate for constant current coulometry.

6. Equivalence Range

Constant current coulometry is conveniently applicable to amounts ranging from a few milliequivalents to about 10^{-4} microequivalent in volumes of the order of 50 ml.[4,11,82]

7. Time

Coulometric titrations are usually completed in a few minutes (100 to 300 sec).

E. ADVANTAGES AND LIMITATIONS

The main advantages of constant current coulometry over conventional titrimetry lie in areas where low concentration or unstable titrants are involved. Other advantages are the ease with which the complete titration can be automated and the fact that no standard solutions are required. The principle limitation of the method is the unavailability of all possible titrants.

1. Accuracy

The accuracy of constant current coulometry is only limited by the inability to maintain 100% current efficiency because of background current. In general, it is subject to less background current than controlled potential coulometry, thus enabling it to be used for the determination of smaller quantities with more convenience and accuracy than potentiostatic coulometry.

2. Precision

The precision obtained in constant current coulometry is limited by (a) the constancy of the current used, (b) the reproducibility of the current measurement, and (c) the reproducibility of the time measurement. The precision normally obtained in constant current coulometry is of the order of 0.1 to 0.3%, comparable to the precision of volumetric analysis. With precautions and simplified equipment, one can measure the number of coulombs (or microequivalents) to about 0.004%,[83] and Tutundzic[84] even recommends that the coulomb replace chemical standards as the ultimate standard for all volumetric work.

F. PHARMACEUTICAL APPLICATIONS

Since titrant is generated, any normal titrimetric procedure can be used. Table 15.1 lists typical examples of the types of titrimetry available, typical generation reactions, and typical titration reactions.

TABLE 15.1: Typical Electrode and Titrant Reactions in Constant Current Coulometry

Type of titration	Typical generation reaction	Typical titration reaction
Redox	$2Br^- - 2e \rightarrow Br_2$ (*titrant*)	$Br_2 + R_2C{=}CR_2 \rightarrow R_2CBrCBrR_2$
	$Ti^{4+} + e \rightarrow Ti^{3+}$ (*titrant*)	$Fe^{3+} + Ti^{3+} \rightarrow Fe^{2+} + Ti^{4+}$
Acid-base	$3H_2O - 2e \rightarrow \frac{1}{2}O_2 + 2H_3O^+$ (*titrant*)	$H_3O^+ + B \rightarrow BH^+ + H_2O$
	$2H_2O + 2e \rightarrow H_2 + 2OH^-$ (*titrant*)	$HA + OH^- \rightarrow A^- + H_2O$
Complexation	$HgY^{2-} + 2e \rightarrow Hg^{2+} + Y^{4-}$ (*titrant*)	$Ca^{2+} + Y^{4-} \rightarrow CaY^{2-}$
Precipitation	$Ag^+ - e \rightarrow Ag^{2+}$ (*titrant*)	$Ag^+ + Cl^- \rightarrow AgCl\downarrow$

The pharmaceutical compounds given as examples in the titrimetric procedures listed in the chapters on (1) precipitation, complex formation, and oxidation-reduction, (2) acidimetry and alkalimetry, (3) nonaqueous titrimetry, and (4) complexometric titrations are directly applicable. Table 15.2 lists the types of titrants that have been electrochemically generated and their literature reference.

TABLE 15.2: Electrogenerated Titrants

Type of titration	Titrant	Literature reference
Redox	Bromine	85–88
	Cerium(IV)	65, 89
	Chlorine	90, 91
	Copper(II)	77
	Hypobromite ion	92
	Iodine	93–95
	Biphenyl radical anion	96
	Chlorocuprous ion	97
	Copper(I)	78
	Tin(II)	98
	Titanium(III)	99
Acid-base	Aqueous acid-base	100, 101
	Nonaqueous acid	102–106
	Nonaqueous base	107–109
Complexation	Cyanide ion	110
	EDTA (ethylenediaminetetraacetic acid)	111
	EGTA [ethylene glycol bis(β-aminoethyl ether)-N,N-tetraacetic Acid]	112
Precipitation	Ferrocyanide ion	113
	Halide ion	114
	Mercury(I)	115, 116
	Mercury(II)	115, 116
	Silver(I)	82, 117
Miscellaneous	Hydrogen	118
	Karl Fischer	119
	MTEG (monothioethylene glycol)	120
	Thioglycollic acid	121

15.4 CHRONOPOTENTIOMETRY[2,11,122]

Chronopotentiometry, which is sometimes called "voltammetry," *at constant current*, is carried out by *controlling the current* to the working electrode. The value of the constant current chosen is greater than the diffusion current of the electroactive species, as shown in Eq. (15.16)

$$i > kC \tag{15.16}$$

The name "chronopotentiometry" is derived from the fact that a constant

current is applied to an electrode and its potential is measured against some reference electrode as a function of time.

A. CURRENT-POTENTIAL-TIME RELATIONSHIP

Since the current is maintained constant by external means, the only variables are potential and time. The potential of the working electrode is in equilibrium with the electrode reactions forced upon the electrode by the electrolysis current.

After a finite time of electrolysis, the electroactive species will be exhausted at the electrode surface. The diffusion rate will not be able to maintain the current because the value of the constant electrolyzing current is greater than the diffusion current of the electroactive species. At this point, another electroactive species (which may be the supporting electrolyte), will start to undergo the electrode reaction, and there will be a rapid change in electrode potential. The time at which this occurs is called the "transition time."

1. One Component

The Sand[10] equation for linear diffusion governs the rate the substance is brought to the electrode:

$$\tau^{1/2} = (\pi^{1/2} n F A D^{1/2} C)/(2i) \tag{15.17}$$

where τ is the transition time in seconds, π is 3.1416, n is the number of electrons involved in the reaction, F is the Faraday in coulombs (96,487 coulombs), D is the diffusion coefficient in square centimeters per second, A is the area of the electrode in square centimeters, C is the bulk concentration of the electroactive species in moles per cubic centimeters, and i is the electrolysis current in amperes.

In analytical practice, the Sand equation is seldom used directly. Instead, the chronopotentiometric constant $(i\tau^{1/2})/C$ is used to empirically calibrate the electrode under a known set of conditions and concentrations for the substance to be determined.

The Sand equation applies strictly to diffusion controlled processes occurring with 100% current efficiency at a plane electrode. This requirement limits the applicability of the Sand equation to the first reaction and to the combined reactions (which must include all the preceding ones) which take place during the electrolysis of a multicomponent system.

Chronopotentiograms (as shown in Fig. 15.8) follow Eq. (15.18), which is commonly called the Karaoglanoff[123] equation:

$$E = E_{1/4} - \frac{RT}{nF} \ln [(\tau^{1/2}/t^{1/2}) - 1] \tag{15.18}$$

The quarter-wave potential, $E_{1/4}$, is the potential at one-quarter the transition time, and when there are no kinetic complications, it is identical to the polarographic $E_{1/2}$.

2. Two Components

If there are two electroactive species in a mixture and their voltammetric half-wave potentials differ by at least 0.1 V, then two distinguishable transition times are observed on the chronopotentiogram. These are used to calculate the concentration of each species. Since the transition time is proportional to the square of the concentration of the electroactive species,

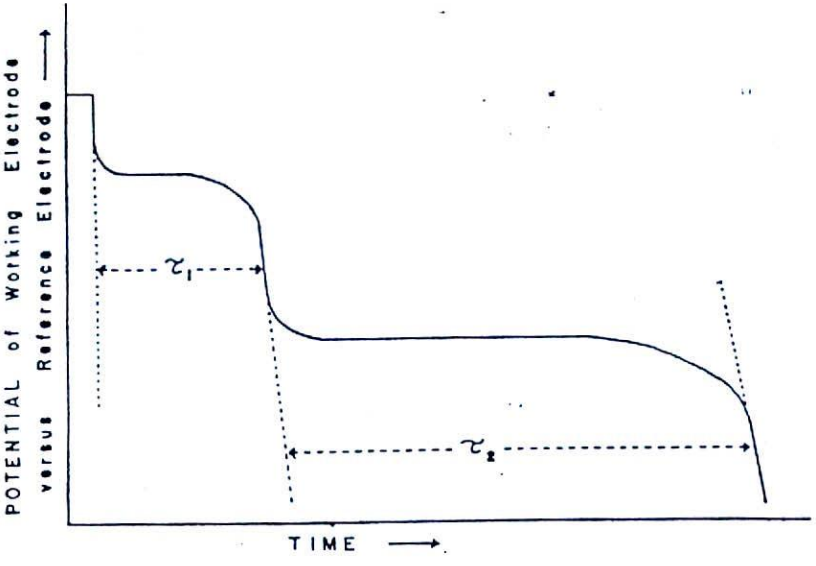

FIGURE 15.8: Chronopotentiogram of a mixture of two compounds having identical concentrations and electrode reactions.

the transition times will not be additive. The combined transition time (τ_{12}) for either consecutive or stepwise reactions (assuming identical diffusion coefficients) is proportional to the square of a pseudo-total concentration (C_{12}^*) as indicated by Eq. (15.19) and (15.20).

$$\tau_{12} = k''(C_{12}^*)^2 \tag{15.19}$$

$$C_{12}^* = n_1C_1 + n_2C_2 \tag{15.20}$$

The transition time (τ_2) for the component which is reduced (or oxidized) after the first component is given by Eq. (15.21).

$$\tau_2 = \tau_{12} - \tau_1 \tag{15.21}$$

The two transition times are compared in Eq. (15.22).

$$(\tau_2/\tau_1) = (\tau_{12}/\tau_1) - 1 = (C_{12}^*/C_1)^2 - 1 \tag{15.22}$$

It follows when n_2C_2 is (a) equal to, (b) twice, and (c) three times n_1C_1, that the second transition time (τ_2) will be respectively (a) 3, (b) 8, and (c) 15 times the first transition time (τ_1). This phenomenon is referred to as an "enhancement" of the second transition time. Figure 15.8 shows the chronopotentiogram of a two component mixture having identical concentrations and electrode reactions.

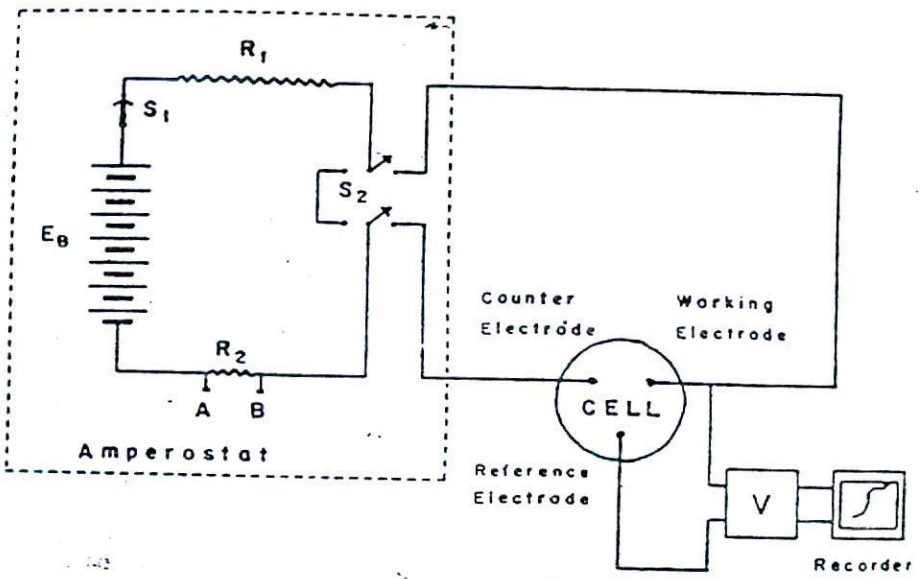

FIGURE 15.9: A simplified circuit for chronopotentiometry where E_B is three 45-V dry-cell batteries, R_1 is a 536,000-Ω, 0.5-W resistor, R_2 is a 4000-Ω precision (±0.05%) resistor, S_1 is an SPST switch, S_2 is a DPDT shorting switch, V is a high-input impedance electronic voltmeter.

B. END-POINT DETECTOR

A voltage indicator or recorder is used as the end-point detector. The input impedance of the device directly connected to the working and reference electrodes must be high enough so that no significant current (with respect to the electrolyzing current) flows in the indicating circuit.

C. CIRCUIT

A simplified circuit for chronopotentiometry is shown in Fig. 15.9. A coulometer is not part of the circuit. The components for chronopotentiometry are:

1. Power Supply

A regulated constant current source similar to the one for constant current coulometry is used.

2. Electrolysis Cell

In chronopotentiometry, the electrolysis cell is similar to that used in controlled potential coulometry. It requires a three-electrode electrolysis vessel containing (a) a working electrode, (b) a reference electrode, and (c) a counter electrode. However, the configuration of the working electrode-counter electrode assembly is critical. It must be designed to maximize the conditions of *linear diffusion*, i.e., diffusion that takes place in a single direction to a planar surface. The surface area of the working electrode must be compatible with current concentration requirements for chronopotentiometry.

D. EXPERIMENTAL CONDITIONS

1. Electrode

a. Material and Potential Range. The electrode (area ca. 0.25 cm²) material and potential range are essentially the same as for controlled potential coulometry. In chronopotentiometry, a platinum electrode is useful as an anode to ca. +1.5 V (vs. SCE),[122] in aqueous systems.

b. Shape. A mathematical analysis of diffusion to a planar electrode is much simpler than for diffusion to cylinders or other geometric configurations. However, cylindrical wire electrodes are easily made, and there are only very minor edge effects when the length of the wire is large compared to its diameter. Although these electrodes are experimentally convenient, the data obtained with them, however, is difficult to interpret because the theoretical transition time equations are quite complex. Lingane[124] introduced a simple empirical correction shown in Eq. (15.23),

$$\tau_{obs} = \tau_{plane}(1 - \beta\tau^{1/2}) \qquad (15.23)$$

where τ_{plane} is the transition time with a plane electrode of equal area, and the constant β depends on the diffusion coefficient of the electroactive species and the radius of the wire electrode.

Solvent

a. Electrolyte, pH, and Oxygen. These requirements are identical to those for controlled potential coulometry.

b. Temperature and Mixing. Effects which will transport electroactive species to the electrode surface by methods other than simple linear

diffusion must be minimized. The temperature therefore must be kept constant and there should be no mixing.

3. Potential

The potential is the variable parameter being measured.

4. End Point

The end point may be a preselected potential (usually the inflection point on the potential-time curve), or it may be graphically determined by methods comparable to the correction for residual currents in polarography.

5. Current Range

Electrolysis currents having magnitudes of 5 μA to 500 μA are normally adequate.

6. Concentration Range

The best results in chronopotentiometry have been obtained for concentrations between 1 and 10 mM, but the method fails at concentrations below about 0.5 mM. The most concentrated solutions successfully studied were 50 mM.

7. Time

Suitable transition times for chronopotentiometric analyses range from about 5 to 25 sec.

E. ADVANTAGES AND LIMITATIONS

Anodic chronopotentiometry appears most advantageous when the technique of oxidative voltammetry fails because of fouling of the electrodes by the products. The much shorter reaction time is responsible for this, but the problem persists[125] for many materials whose reaction products coat the electrode with insoluble polymeric material.

1. Accuracy

The accuracy of chronopotentiometry is limited solely by the inability to maintain 100% current efficiency. At short transition times, (less than 1 sec), background currents[126] are due to (a) charging of the electrical double layer, (b) adsorption of electroactive species, (c) surface oxidation or reduction of the working electrode (platinum), and (d) impurities in solution. At long transition times, (greater than 25–50 sec), errors are introduced[127] because

of (a) natural convection due to density gradients and (b) unavoidable external laboratory vibrations which disturb the diffusion layer.

2. Precision

The precision obtained in chronopotentiometry is limited by (a) the constancy of the electrolysis current used, (b) the constancy and reproducibility of the temperature during electrolysis, (c) the reproducibility of the current measurement, and (d) the reproducibility of the time measurement. The precision normally obtained in chronopotentiometry is about 1%.

F. PHARMACEUTICAL APPLICATIONS

Although very few pharmaceutical compounds have been studied, chronopotentiometry should be applicable to polarographically or voltammetrically electroactive species. It should be especially useful for antioxidants and related compounds.

Chronopotentiometric studies have been reported for cerium,[128] bromide,[129] copper,[130] iodide,[127] iron,[124,130] lead,[127,130,131] oxygen,[132] silver,[127] zinc,[130] adenine,[134] anthracene,[133] antioxidants and antiozonants,[125] aromatic amines,[135] ascorbic acid,[134] benzoquinone,[134] catechol,[136] hydrazine,[137] hydroquinone,[127,134,136] hydroxylamine,[138] hydrogen peroxide,[139] mercaptobenzothiazole,[140] oxalic acid,[141] phenols,[135] phenylenediamine,[125,136] phenylmercuric ion,[57] riboflavin,[142] sulfa drugs,[143] sulfanilamide,[133,134] toluene 2,4-diamine,[140] and triethylamine.[144]

15.5 EXPERIMENTAL PROCEDURES

A. CONTROLLED POTENTIAL COULOMETRY

Ascorbic acid is determined by controlled potential coulometry using the general procedure of Santhanam and Krishnan[16] (courtesy of *Analytical Chemistry*).

1. Apparatus

a. Potentiostat. A manually controlled potentiostat (current capacity ca. 100 mA) shown in Fig. 15.4 is used.

b. Electrodes. Concentric cylinders of thick platinum gauze with reinforced edges serve as anode and cathode. The former is 2.5 cm in diameter, 4 cm high, and the latter, 5 cm in diameter and 5 cm high. The reference electrode is a standard saturated calomel electrode placed in a sleeve (filled with a solution of 1 *M* potassium nitrate) terminated with a fine sintered-glass disk. This combination is placed in the center of the cylindrical anode.

c. Cell. The electrolysis cell is a 250-ml open beaker provided with magnetic stirring.

d. End-Point Detector. A precision 0.100-Ω resistor in conjunction with a 10-mV strip-chart recorder (full-scale reading 100 mA) with a chart speed of 20 in./hr is used to determine the end point.

e. Coulometer. The coulometer is a nitrogen-hydrogen type[25] with a 5-ml burette containing 0.1 *M* hydrazine sulfate.

2. Reagents

The supporting electrolyte is a potassium biphthalate buffer of pH 6.0. It is prepared by diluting 500 ml of 0.1 *M* potassium biphthalate with about 455 ml of 0.1 *M* sodium hydroxide and checking the final pH with a glass-calomel electrode combination. The ascorbic acid is USP grade.

3. Procedure

Add about 180 ml of the buffer solution to the cell and electrolyze at an anode potential of +1.2 V (vs. SCE) until the current falls to a steady low background value. This removes any oxidizable impurities in the supporting electrolyte and avoids the need for background correction. Transfer into the preelectrolyzed solution a weighed sample of about 15 mg of ascorbic acid. Zero the gas coulometer. Start the electrolysis at +1. 1V (vs. SCE). Simultaneously start the strip-chart recorder. Continue the electrolysis until the current is about 1 mA. This should take about 30 min.

4. Calculation

Assuming a two-electron process, calculate the amount of ascorbic acid titrated using the quantity of electricity passed calculated from (a) the gas coulometer reading and (b) an integration of the current-time curve on the recorder.

B. CONSTANT CURRENT COULOMETRY

Isoniazid (isonicotinic acid hydrazide) is analyzed by constant current coulometry with electrolytically generated bromine. The following is the general method of Olson[85] (courtesy of *Analytical Chemistry*).

1. Apparatus

a. Amperostat. The amperostat (Fig. 15.6) is a constant current power supply which operates at 20 mA.

b. Electrodes. The generating electrodes are a pair of 1 cm^2 platinum foil electrodes. Isolate the cathode from the test solution by a sintered-glass disk.

c. Cell. The titration vessel is a 100-ml beaker provided with magnetic stirring.

d. End-Point Detector. The end point is determined amperometrically. A pair of concentrically wound platinum spirals are the indicating electrodes, and a potential of 0.2 V is impressed across them.

e. Coulometer. An electric stop clock with a 1000-sec range and capable of being read to 0.1 sec serves as the coulometer.

2. Reagents

Isoniazid is USP grade. The electrolysis solvent is a solution of 30 ml of acetic acid, 13 ml of methanol, and 7 ml of 1 *M* aqueous potassium bromide.[145]

3. Procedure

Close switches S_1 and S_2 (Fig. 15.6) and allow the amperostat to run for 30 min to come to thermal equilibrium. Determine the current by measuring the iR drop across resistor R_2 (at points A and B) with a Leeds & Northrup student K potentiometer. The setting of the dummy resistor R_3 can be determined by observing whether the current changes significantly when opening and closing switch S_2 with the filled electrolysis vessel in the circuit. Transfer a weighed sample of about 2 mg of isoniazid to the cell. Add 50 ml of electrolysis solvent, insert the electrode assembly, and titrate (by opening switch S_2) at a constant current of about 20 mA until the microammeter (which initially reads about zero) remains at the cutoff current (10 μA) for at least 30 sec, then close switch S_2. Approximate time is 5 min. Repeat the procedure for the solvent alone.

4. Calculation

Calculate the amount of isoniazid using the blank correction for the solvent. Assume a four-electron reaction.

C. CHRONOPOTENTIOMETRY

Sulfa drugs may be determined by chronopotentiometry using the general procedure of Voorhies and Furman[133] (courtesy of *Analytical Chemistry*).

1. Apparatus

a. Amperostat. The amperostat (Fig. 15.9) is a constant current power supply operating at ca. 0.25 mA.

b. Electrodes. A thick platinum wire, 0.2 cm in diameter and surface area 1.3 cm^2 serves as anode, platinum gauze as the cathode, and a saturated calomel electrode as reference electrode.

c. Cell. The electrolysis vessel is a 100-ml beaker provided with magnetic stirring.

d. End-Point Detector. (1) Voltmeter. A high-input impedance electronic voltmeter such as a pH meter with an output for a recorder is used to measure the potential of the working electrode.

(2) Recorder. A strip-chart recorder having a 1 sec full scale response and a chart speed of 8 in./min (with a full-scale sensitivity suitable for use with the pH meter) is used.

2. Reagents

The supporting electrolyte is 1 *M* perchloric acid solution. The sulfisoxazole is USP grade.

3. Procedure

Close switches S_1 and S_2 (Fig. 15.9) and allow the amperostat to operate a few minutes to come to equilibrium. Determine the current by measuring the iR drop across resistor R_2 (at points A and B) with a Leeds & Northrup student K potentiometer. Transfer a weighed sample of 10 mg of sulfisoxazole into the electrolysis vessel. Add 50 ml of 1 *M* perchloric acid solution.

Wash the working electrode with chromic acid for about 30 sec, rinse with distilled water and wipe dry. Insert the electrodes into the test solution and stir the solution briefly. One minute after the stirring is stopped, start the recorder chart drive and apply a constant current of ca. 0.25 mA to the platinum electrodes by opening switch S_2. Record the chronopotentiogram. The complete chronopotentiogram should take about 1 min. Close switch S_2 on completion of the chronopotentiogram. Repeat this operation for samples of 15 mg and 20 mg.

4. Calculation

Using a graphical technique, determine the $E_{1/4}$ and $\tau^{1/2}$ for each chronopotentiogram. Calculate the chronopotentiographic constant $(i\tau^{1/2})/C$ for sulfisoxazole for the particular electrolysis cell used.

QUESTIONS

Q15.1. What is the purpose of the supporting electrolyte?
Q15.2. What functions do electrodes serve?
Q15.3. Write the equations for the electrode reactions generating four different types of titrants.
Q15.4. What experimental factors influence electrochemical techniques?

Q15.5. When is back titration necessary in constant current coulometry?
Q15.6. Compare the chronopotentiometric $E_{1/4}$ with the polarographic $E_{1/2}$.
Q15.7. Compare the concentration range served by each of these methods.
Q15.8. Compare the operating time necessary for analytical determinations by each of these methods.
Q15.9. Describe what factors controlled potential coulometry, constant current coulometry, and chronopotentiometry have in common.
Q15.10. What relationship exists between the electrolysis current, and the diffusion current of the electroactive species in coulometric methods and chronopotentiometry?
Q15.11. Compare coulometry with titrimetry.
Q15.12. Which of the techniques described in the chapter can quantitatively assay substances which are not electroactive?
Q15.13. What type of compounds are electroactive?
Q15.14. Contrast the end-point methods available for constant current coulometry with those for controlled potential coulometry and chronopotentiometry.
Q15.15. Compare the behavior of a two component electroactive mixture in controlled potential coulometry, constant current coulometry, and chronopotentiometry.
Q15.16. What are the advantages and limitations of the various methods described in this chapter?
Q15.17. Describe possible reasons for the use of an external generation of chemical titrant.
Q15.18. What is transition time enhancement?
Q15.19. Why are the transition times of a stepwise reaction requiring the same number of electrons not identical?
Q15.20. Compare the effect of temperature and mixing in coulometry and chronopotentiometry.
Q15.21. What is voltammetry?
Q15.22. What is amperometry?
Q15.23. Derive the equation for the electrolysis current decay-rate constant k' for controlled potential coulometry.
Q15.24. What is the relationship between the electrolysis current to concentration proportionality constant k and the decay-rate constant k' in controlled potential coulometry?
Q15.25. Derive the Sand equation.

PROBLEMS

P15.1. Given that the diffusion coefficient is 6.9×10^{-6} cm^2/sec, the area 50 cm^2, the total volume 100 cc, and the diffusion layer 2.3×10^{-3} cm, what is the electrolysis current decay-rate constant k'? How long will it take to electrolyze 50, 95, or 99% of the electroactive substance by controlled potential coulometry?
P15.2. In the just mentioned conditions, if there were 0.17 meq of electroactive substance initially present, how large would the initial electrolysis current be?
P15.3. Calculate the time necessary to reach the end point when titrating 30 μmoles of an olefin with electrogenerated bromine using 10 mA of current?

P15.4. Given that the diffusion coefficient is 7.96×10^{-6} cm²/sec, the area 1.0 cm², and n is 2, what is the value for the chronopotentiometric constant $i\tau^{1/2}/C$? If 500 μA electrolysis current for a 2.59 mM concentration of an electroactive species was used, what would the transition time be?

P15.5. Given substance a has a diffusion coefficient of 7×10^{-6} cm²/sec, the bulk concentration is 2 μmoles/cc, and 2 electrons are involved in its reduction, and substance b has a diffusion coefficient of 7×10^{-6} cm²/sec, the bulk concentration is 1 μmole/cc, and 1 electron is involved in its reduction, what is the transition time ratio of substance a to substance b when substance a is reduced (a) first or (b) second?

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