THEODORE SHEDLOVSKY

1898—1976

A Biographical Memoir by

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Biographical Memoir

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In April 1953, at the one hundred and third meeting of the Electrochemical Society, Theodore Shedlovsky opened a symposium on Electrochemistry in Biology and Medicine with the following introduction:

Electrochemistry is concerned with the electrical properties and behavior of substances and with the transformation of chemical energy into electrical energy or vice versa. It is related to biology and medicine in two ways. First, it provides powerful laboratory methods and tools for the study of biologically important substances, such as viruses, hormones, enzymes and other proteins, and also for the determination in biological environments of such factors as acidity, oxidation-reduction, ionic mobility, activity and diffusion, dielectric constant and dipole moments. Second, living organisms and in fact all living cells are complicated electrochemical systems capable of transforming chemical energy and ionic transport into electrical signals. With appropriate apparatus the neurophysiologist may examine such electrical signals to learn what he can about the functions of nerve and muscle. The medical clinician, armed with a substantial background of correlated, empirical knowledge, observes the electrical signals from the heart or from the brain and thus is aided in arriving at a diagnosis. Living matter or a living cell is not a mere assembly of chemical compounds. It is an oriented, dynamic system of complex materials in constant interaction with its environment, a complex chemical laboratory manufacturing many compounds no chemist has yet been able to synthesize, and electrochemical in many if not perhaps all of its functions. Between the inside and the outside of a living cell there exists normally an electrical potential usually of about a tenth of a volt. It is true of plant cells as well as cells of mammals,
birds, or fishes. This is the so-called "resting" potential. In certain cells like nerve cells, this potential may be quickly altered and restored again, giving rise to electric "action potentials" in response to various stimuli. In nerve, this happens within a few milliseconds and is in the nature of electric transients. The theory of the fundamental electrochemical mechanism underlying these bio-electric phenomena is now an active subject of research.

Development of precise electrochemical methods and their application to biochemical problems were Shedlovsky's life work at the Rockefeller Institute for Medical Research (since 1965, The Rockefeller University). In 1926, W. J. V. Osterhout invited Duncan A. MacInnes (then professor of chemistry at the Massachusetts Institute of Technology) to come to Rockefeller and organize a research group to work on the physical chemistry of electrolytic solutions. MacInnes accepted; his first appointee (1927) was Shedlovsky, who had been one of his graduate students at MIT. Lewis G. Longsworth joined the group in 1928, first as a fellow of the National Research Council; he subsequently became a member of the Rockefeller staff. Within five or six years, the triumvirate of MacInnes, Shedlovsky, and Longsworth created at Rockefeller one of the world's outstanding centers of electrolyte research. Their classical contributions included work on thermodynamic properties of electrolytic solutions, conductance, diffusion, and electrophoresis. Shedlovsky chose conductance as his special field of interest and by the mid-1930's was generally recognized as an authority on the subject. In addition to his work on inorganic electrolytes, he collaborated with a number of bio-oriented colleagues on work with biochemical systems. His tangible contributions to science are characterized by ingenuity in design of experiments and apparatus, precision in execution, and clarity of thinking and presentation. Equally valuable, however, were his intangible contributions: he served as an interpreter between the phys-
ical chemist and the biochemist, bringing to each field ideas from the other. He also had an uncanny instinct for bringing together people who had problems with people who had ideas and suggestions.

Shedlovsky had many interests besides science. He was fluent in Russian, German, and French (his elementary schooling was in Paris). He was an expert chess player, phenomenally good in rapid transit play, and had given checkmate to masters. An ardent music lover, he established and directed The Rockefeller University Concerts, which have been held monthly in Caspary Auditorium every year since 1958. In 1965, he founded the Rockefeller Children’s School for children aged three to seven whose parents are members of the faculty, staff, and student body of the University. In 1975, in recognition of his contributions to science and to the life at Rockefeller, he was awarded the honorary degree of Doctor of Science. In the citation at commencement, Professor Vincent P. Dole said:

Professor Theodore Shedlovsky combines many rare qualities. In his scientific work he is distinguished as an electrochemist. . . . There is much to admire in his scientific achievements, and yet they are not the only reason why we honor him today. As a person, Ted Shedlovsky represents something even rarer than master electrochemist—he is a special person who makes the world around him richer. He has launched conferences, started and guided our remarkable concert series, created a school for University children and counseled many of us. No wonder he has so many friends.

As background for a review of Shedlovsky’s career of a half century at Rockefeller, an introductory discussion of electrolytes and electrochemistry is in order. Electrolytic solutions are systems in which the electric current is carried by ions; ions are molecules (monatomic or polyatomic) that are electrically charged. The simplest example is a solution of salt in water: the current is carried by hydrated sodium ions
(sodium atoms that have lost an electron and are therefore positively charged) and chloride ions (chlorine atoms that have gained an electron and are negatively charged). The ions of biochemical electrolytes are much more complicated: a protein is a polyamide, a long sequence of condensed α-amino acids,

\[ \ldots -\text{NH} \cdot \text{CHR'} \cdot \text{CO} - \text{NH} \cdot \text{CHR''} \cdot \text{CO} - \text{NH} \cdot \text{CHR'''} \cdot \text{CO} - \ldots, \]

where the units containing the R groups are selected by biosynthesis from about twenty amino acids whose general formula is \( \text{H}_2\text{N} \cdot \text{CHR} \cdot \text{CO}_2\text{H} \). Some of the R groups are ionogenic; for example, glutamic acid \( \text{HO}_2\text{C(CH}_2)_2\text{CH(NH}_2\text{)CO}_2\text{H} \), where \( R = -(\text{CH}_2)_2\text{CO}_2\text{H} \), contains a terminal carboxyl group that generates the negative carboxyl ion \( -\text{CO}_2^- \); or lysine \( \text{H}_2\text{N(CH}_2)_4\text{CH(NH}_2\text{)CO}_2\text{H} \), which forms the positive ammonium ion \( -(\text{CH}_2)_4\text{NH}_3^+ \). Therefore, depending on the relative number of positive and negative ionogenic R's in the protein and on the pH (a measure of the hydrogen ion concentration) of the buffer (serum, for example) in which the protein is dissolved, the protein may have either a net positive or negative charge. Such charged macromolecules are called polyelectrolytes; proteins and the two types of nucleic acids (ribonucleic acid [RNA] and deoxyribonucleic acid [DNA]) are the most important categories of biochemical polyelectrolytes. (We shall be concerned here only with the properties of electrolytic solutions, usually aqueous, and exclude as irrelevant fused salts and certain solids, which also carry the electric current by ionic transport.)

The properties of electrolytic solutions depend on the chemical structure and composition of the electrolyte and on its concentration. The velocity \( v \), imparted to an ion by a given electrical potential across two electrodes immersed in the solution, is proportional to the charge on the ion because
the force driving the ion is $Xze$, field strength times net charge $ze$ ($e =$ unit charge). The velocity $v = Xze/f$ is less the larger the ion because the friction coefficient $f$ increases with increasing size of the moving particle. The electrophoretic velocity of a polyelectrolyte ion is a measure of its charge and size; and also of its shape, because the friction coefficient for an ellipsoid, for example, is greater than for a sphere of equal volume. A protein molecule in acid solution (pH < 7) has a net positive charge; in basic solutions (pH > 7), the positive $-\text{NH}_3^+$ ions are converted into neutral amino-groups, and the neutral carboxyl groups become negative $-\text{CO}_2^-$ groups. Consequently, there is a value of pH at which the mobility becomes zero (net charge equals zero); that value (the isoelectric point) is characteristic for the protein.

Solutions of different electrolytes at the same concentration show different electrical conductivities. Aqueous solutions of electrolytes are classified traditionally as “strong” and “weak”; for a given stoichiometric concentration, the latter are much poorer conductors, because only part of the solute is present as ions. For example, acetic acid in water exists mostly as hydrated neutral CH$_3$CO$_2$H·H$_2$O molecules, and only a small fraction dissociates into conducting acetate CH$_3$CO$_2^-$ and hydronium H$_3$O$^+$ ions. Determination of the dissociation constants of biochemical acids is an electrochemical problem. The strong electrolytes exist as ions in water; salt water contains no neutral NaCl molecules, but only sodium Na$^+$ and chloride Cl$^-$ ions. Measurement of the dependence of conducting ability of electrolytes in general on concentration and its theoretical description form a major chapter of electrochemistry. Shedlovsky's contributions, as shown by the titles listed in the bibliography, are on conductance, dissociation constants, and electrophoresis.

In principle, the experimental determination of the conductivity of an electrolytic solution is simple: one measures
the resistance $R_x$ between a pair of electrodes immersed in the solution by means of a bridge circuit, and calculates the specific conductance $\sigma$ (the reciprocal of the resistance of a cube of solution one centimeter on a side) by dividing the cell constant $k$ by $R_x$, $\sigma = k / R_x$. (The cell constant for parallel plate electrodes of area $A$ placed at a distance $d$ [with $d^2 << A$] is $k = d/A$.) The classical method used dipping electrodes for the cell and the Kohlrausch slide wire for the bridge: precision of several percent in $\sigma$ can be easily obtained, and with care a precision of 0.1–0.2% was attainable. Shedlovsky set a precision of 0.01–0.02% as his goal. In 1930 he published two papers: "A Screened Bridge for the Measurement of Electrolytic Conductance," and "A Conductivity Cell for Eliminating Electrode Effects in Measurements of Electrolytic Conductance." Using this bridge, he and his co-workers determined the conductance of a wide variety of electrolytes to the desired precision; extrapolation of the data to evaluate limiting conductance (vide infra) was made using the Shedlovsky 1931 equation.

The screened bridge made possible for the first time measurements of electrolytic conductances by alternating current to one part in 100,000 (0.001%); using it, the experimenter has complete confidence in the electrical data, and the precision in equivalent conductance $\Lambda = 1000\sigma/c$ becomes the precision in concentration $c$ (about 0.01%) and in temperature control ($\sigma$ varies by about 2% per degree, so thermostating the solution to ±0.005° fixes $\Lambda$ to 0.01%). The necessity of screening the bridge is a consequence of using audio-frequency alternating current in measuring electrolytic conductance; it must be used because direct current would produce irreversible electrochemical reactions at the electrodes, thereby introducing errors of unknown magnitude. (Direct current can be used only with a few electrolytes for which reversible electrodes can be made; for example, silver-silver
chloride electrodes for chloride solutions.) The Wheatstone bridge may be pictured as follows: imagine four points A, B, C, and D connected by resistances $R_{AB}, R_{BC}, R_{CD},$ and $R_{DA}$. Let $R_{AB} = R_{BC}$. If direct current is fed in at A and C, and $R_{DC}$ (a calibrated rheostat) is varied, the voltage across B and D will go through zero when $R_{DC}$ equals the unknown resistance $R_{DA}$. But if alternating current is applied across A and C, the condition for zero voltage across B and D is $Z_{AB} / Z_{BC} = Z_{AD} / Z_{DC}$, where $Z_{AB}$ is the impedance between the terminals A and B, etc. Impedance is made up of resistive, capacitative, and inductive elements; the last two play no role in direct current circuitry. Suppose the conductance cell is connected to the terminals A and D. Electrically, it acts as a resistance and capacity in parallel, with capacity paths to ground. There exist in the other three arms of the bridge distributed capacity to ground and resistance-capacity paths among the three elements. Consequently, at zero voltage across B and D, the resistance component of $Z_{CD}$ in general does not equal the resistance of the electrolyte in the cell connected to A and D. Shedlovsky made a theoretical analysis of the rather complicated circuits just described, which led to a bridge design in which the ratio arms AB and BC were symmetrically shielded; the measuring rheostat connected across C and D, and the various lead wires were also screened. All shields were connected to ground (earth point E). Then a Wagner ground was added, which permits the operator to bring points B and D to the potential of E. At final balance, the voltage across B and D is zero and both B and D are at ground potential: under these conditions, the resistance component of $Z_{DC}$ exactly equals the resistance of the electrolyte in the cell. Screening brought two additional advantages: first, effects of stray currents from other electrical equipment in the laboratory were avoided; and second, bridge balance became independent of the position of the operator (for an un-
screened bridge, the electrical capacity between the elements of the bridge and the body of the operator also is a path for stray currents to ground).

Shedlovsky also designed a conductance cell that eliminated errors inherent in the dipping electrodes. Cell constants are usually determined by measuring the resistance $R$ of a cell containing a standardizing solution of known specific conductance $\sigma_s$; $k = R\sigma_s$. For dipping electrodes, somewhat different values (±1%) were found for a given cell when different calibrating solutions were used; obviously, such cells could not deliver data reliable to ±0.01%. Shedlovsky showed that the variation in apparent cell constant with resistance was caused by a series capacity-resistance circuit, which shunted the resistance of the solution between the electrodes. The capacity was the insulation surrounding the lead wires to the electrodes; the resistance was that of the solution between the immersed insulation and the electrodes. This circuit is electrically equivalent to a resistance in series with the electrolytic resistance plus a parallel capacitance. By placing the electrodes in a capsule attached to the container for the solution, the leads to the electrodes do not pass through the solution, and the impedance of the shunt becomes so high that its effect becomes negligible. The value of $k$ for cells so constructed is completely independent of the resistance of the calibrating solution. The principle of this design of conductance cell was universally adopted by other workers in the field of conductance. Several of the conductance cells used by Shedlovsky are in the collection of instruments and apparatus on display in Caspary Hall at Rockefeller.

Conductance measurements are made in order to determine parameters that are characteristic of a given electrolyte. One of these is $\Lambda_0$, the limiting equivalent conductance, which
is proportional to the velocity of the ions at infinite dilution. The observed equivalent conductance $\Lambda$ of strong electrolytes decreases with increasing concentration because the long-range electrostatic forces between the ions reduce their mobility. In order to obtain $\Lambda_0$, the experimenter measures conductance at a series of concentrations and then extrapolates to zero concentration. Shedlovsky introduced in 1932 a method of extrapolation that has since been widely used. Kohlrausch (1900) found empirically that at low concentrations the observed values of $\Lambda(c)$ approached linearity on a $\Lambda-c^{1/2}$ plot; Debye and Hückel (1923) gave a theoretical explanation of this behavior. Onsager (1927) succeeded in calculating the value of the coefficient $S$ in the equation

$$\Lambda_{LT} = \Lambda_0 - Sc^{1/2}$$

for the limiting tangent to the Kohlrausch plot. The coefficient $S$ was derived by theoretical treatment of the long-range interionic forces; it is the sum of two terms: $\alpha\Lambda_0$, the relaxation field effect, and $\beta$, the electrophoretic coefficient. At non-zero concentrations,

$$\Lambda(c) = \Lambda_0 - Sc^{1/2} + F(c),$$

that is, the observed conductance curve was concave-up, above the limiting tangent. For very dilute solutions ($<0.01$ normal for 1-1 salts in water), $F(c)$ appeared to approach linearity in concentration, and the equation

$$\Lambda = \Lambda_0 - Sc^{1/2} + Ac$$

was used to extrapolate observed conductances to zero concentration. But working at such low concentrations involved
many experimental difficulties, and some uncertainty in the absolute value of $\Lambda_0$ resulted. Shedlovsky rearranged equation (2) to the form

$$\Lambda_0 = \left( \Lambda + \beta \sqrt{c} \right) / (1-\alpha \sqrt{c}) - Bc = \Lambda_0' - Bc$$

and showed that $\Lambda_0'$, which contains the observed equivalent conductance $\Lambda$ and the theoretically predictable terms $\alpha \sqrt{c}$ and $\beta \sqrt{c}$, was linear in concentration up to about 0.1 normal for 1-1 salts in water (about 6% by weight for sodium chloride). The conductance of a number of 1-1 electrolytes (potassium chloride, sodium chloride, hydrochloric acid, potassium nitrate, silver nitrate, and lithium chloride [1932]) was measured over the concentration range 0.00003–0.10 normal to a precision of about 0.02%. The values of limiting conductances obtained using equation (4) for the data over the entire concentration range agreed exactly with those obtained using equation (3) over the lower range (0.00003 < $c$ < 0.01); this result showed that it was not necessary to measure conductances at extreme dilutions in order to obtain reliable values of $\Lambda_0$. It is sufficient to cover the approximate range 0.005 < $c$ < 0.10, thereby avoiding all the experimental difficulties that beset work with highly dilute salt solutions.

The term $F(c)$ in equation (2) represents the deviation of the observed conductance curve from the limiting tangent, $\Lambda_{LT} = \Lambda_0 - S \sqrt{c}$. Derivation of the functional form of $F(c)$ is a much more difficult problem for the theoretician than prediction of the value of $S$, because it involves the integration of a set of nonlinear differential equations; however, Onsager (1927) showed that the leading terms of $F(c)$ should be of order $c \log c$ and $c$. Shedlovsky (1934) measured the conductances of magnesium, calcium, strontium, and barium chlorides over the concentration range 0.0002 < $c$ < 0.1 normal.
Using the data at lower concentrations and equation (4), he obtained values of $\Lambda_0$ for the four 2-1 salts. He then demonstrated the existence of the $c \log c$ term by showing that a plot of $(\Lambda_0' - \Lambda_0)/c$ against $\log c$ for the whole set of data approached linearity below about 0.01 normal, thereby establishing the functional form

$$\Lambda = (\Lambda_0 - \beta c^{1/2})/(1 + \alpha c^{1/2}) - Bc + Dc \log c + \ldots$$  \hspace{1cm} (5)$$

predicted by Onsager. Furthermore, the sequence of his empirical values for the coefficients $D$ confirmed the theoretical expectation that $D$ should decrease with increasing size of the cation.

Equations (4) and (5) are valid for strong electrolytes; the corresponding conductance curves lie above the limiting tangent on a $\Lambda - c^{1/2}$ plot. But for many electrolytes, the observed conductance curve lies below the limiting tangent: examples are carboxylic acids and amines in water, or salts in solvents of lower dielectric constant. After an expository introduction, Shedlovsky’s many contributions to the field of weak electrolytes will next be reviewed.

Specific conductance is defined as the ratio of current density $i$ to field strength $X$; current density is the total charge carried per second across the area of one square centimeter perpendicular to the direction of the field:

$$\sigma = i/X = \Sigma n_i e_i v_i / X,$$ \hspace{1cm} (6)$$

where $n_i$ is the number per unit volume of ions of species $i$ carrying a charge $e_i$ and moving with a velocity $v_i$ cm/sec. Therefore, equivalent conductance $\Lambda = 10^3 \sigma / c$ is given by

$$\Lambda = A \Sigma n_i e_i v_i / c,$$ \hspace{1cm} (7)$$
where \( u_i = v_i/X \) is the velocity for unit field (one volt/cm) and \( \Lambda \) is a known constant of proportionality. For strong electrolytes at low concentrations, all the solute is assumed to contribute to transport of charge; for 1-1 electrolytes, the number of cations (or anions) per unit volume is simply \( n_i = Nc/1000 \), where \( N \) is Avogadro's number and \( c \) is equivalents of salt per liter. Hence, \( \Lambda \) is proportional to \( \Sigma u_i \). As mentioned above, the electrostatic forces between the ions reduce their mobility from \( u_i^0 \), the value for an isolated ion, by an amount proportional to the square root of concentration; the corresponding conductance function is equation (2). But not all the solute is present as ions in the case of weak electrolytes. Acetic acid, for example, in aqueous solution can rearrange to an ion pair

\[
[\text{CH}_3\text{CO}_2\text{H} \cdot \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ \cdot \text{CH}_3\text{CO}_2^-],
\]

which dissociates into the free hydronium ions and acetate ions that carry the electric current. Denote by \( \gamma \) the fraction of solute that is dissociated; then \( \gamma = n_i/(Nc/1000) \) and the concentration \( c_i \) of free ions is \( c\gamma \). Equation (7) becomes:

\[
\Lambda = \Lambda' \gamma \Sigma u_i = \gamma (\lambda_1 + \lambda_2),
\]

where \( \lambda_1 \) and \( \lambda_2 \) are the single ion conductances of cation and anion respectively; \( \lambda_i = \mathcal{F} u_i \), where \( \mathcal{F} \) is the Faraday equivalent. The retarding effects on mobility of the interionic forces is proportional to \( (c\gamma)^{1/2} \); for low concentrations, the conductance equation, therefore, is

\[
\Lambda = \gamma [\Lambda_0 - S(c\gamma)^{1/2}].
\]

The law of mass action for the postulated equilibrium between neutral molecules and free ions,
relates $\gamma$ and the stoichiometric concentration $c$ by the equation

$$K = c\gamma f/(1-\gamma),$$

where $K$ is the dissociation constant of AB and $f$ is the ionic activity coefficient. For low concentrations, the latter may be approximated by the Debye-Hückel limiting law

$$-\ln f = C(c\gamma)^{1/2},$$

where $C$ is a known coefficient that depends on dielectric constant and temperature. Equations (9), (11), and (12) can be solved for the two parameters $A_0$ and $K$, which are characteristics of the electrolyte AB, given a set of conductance data. Equation (9) is the Fuoss-Kraus conductance function (1933); it uses the limiting law (1) as an approximation for the interionic effects on mobility. This approximation is valid only below ionic concentrations $c_i \approx 0.001$ normal. Shedlovsky (1938) discovered that conductance data for 1-1 salts could be reproduced to high precision by the equation

$$\Lambda = \Lambda_0 - \Lambda Sc^{1/2}/\Lambda_0$$

up to concentrations as high as $c_i \approx 0.01$, ten times as far as (1) was usable. Equation (13) rearranges to

$$1/\Lambda = 1/\Lambda_0 + (S/\Lambda_0^2)c^{1/2}.\quad (14)$$

For incompletely dissociated electrolytes ($c_i = c\gamma$), (14) becomes

$$\Lambda = \gamma\Lambda_0/[1 + (S/\Lambda_0)(c\gamma)^{1/2}], \quad (15)$$
which is a quadratic in $\gamma^{1/2}$, in contrast to (9), which is a cubic. The system of equations (15), (11), and (12) is therefore much easier to solve for $\Lambda_0$ and $K$ than the system (9), (11), and (12), and is usable over a much wider range of ionic concentrations. It was used by Shedlovsky and by many others to derive values of limiting conductance and dissociation constants for a wide variety of electrolytes.

The above method derives $\Lambda_0$ and $K$ for a given electrolyte from conductance data on that electrolyte. It is based on the semi-empirical equation (13) and on the value of $S$ that was calculated for the primitive model (rigid charged spheres of diameter $a$ in a continuum, which is described electrostatically by the dielectric constant of the pure solvent and hydrodynamically by the viscosity). MacInnes and Shedlovsky (1931) devised a method of obtaining $\Lambda_0$ and $K$ that is independent of model and, therefore, does not depend on any theoretical treatment of interionic forces. It is based on the Kohlrausch law of independent mobility (i.e., additivity of equivalent conductances). For a completely dissociated electrolyte, $\gamma = 1$ and $\Lambda = \Lambda_0[1 - G(c)]$, where $G(c)$ represents the total effect of interionic forces on mobilities. For a weak electrolyte (for example, acetic acid), the equivalent conductances of a mole of the electrolyte at concentration $c$ is $\Lambda(c) = \gamma \Lambda_0 [1 - G(c\gamma)]$; the equivalent conductance $\Lambda'$ of a mole of a hypothetical completely dissociated acetic acid at the ionic concentration $c\gamma$ would be

$$\Lambda'(\text{HAc}) = \Lambda_0[1 - G(c\gamma)].$$

Therefore, $\gamma = \Lambda'(\text{HAc})/\Lambda(c)$; the unknown factor $\Lambda_0[1 - G(c\gamma)]$ divides out. Now $\Lambda'(\text{HAc})$ cannot be determined directly, but, by use of the additivity rule,

$$\Lambda'(\text{HAc}) = \Lambda(\text{HCl},c\gamma) - \Lambda(\text{NaCl},c\gamma) + \Lambda(\text{NaAc},c\gamma),$$
where the symbols $\Lambda(AB, c\gamma)$ represent the equivalent conductances of the completely dissociated electrolytes $AB$ at stoichiometric concentrations $c\gamma$. In other words, one can synthesize numerical values of $\Lambda'(HAc)$ by interpolation from conductance data on hydrochloric acid, sodium chloride, and sodium acetate, and then calculate $\gamma$. A plot of the logarithm of $c\gamma^2/(1-\gamma)$ against $(c\gamma)^{1/2}$ was found to be linear up to 0.01 normal solutions of acetic acid, with the theoretical slope $C$ of (12); values of $K$ calculated by (11) averaged to $1.753 \times 10^{-4}$. This result was in perfect agreement with the value reported by Harned and Owen (1930), who had used an entirely different method to determine the dissociation constant of acetic acid (e.m.f. measurements on cells without liquid junction). Later (1935), the same method was used to determine the first dissociation constant of carbonic acid from conductance data on potassium bicarbonate, potassium chloride, and hydrochloric acid. (Carbonic acid, $H_2CO_3$, is the weak acid formed from water and carbon dioxide, one of the end products of metabolic oxidation.)

The two methods described above for determining dissociation constants of weak electrolytes (based on equations [15] and [17]) were applied to a variety of systems that can serve as physicochemical models for biochemical systems. Very roughly described, the latter are assemblies of cells containing aqueous solutions and suspensions inside nonaqueous membranes; a study of the behavior of electrolytes in nonaqueous media therefore became part of the research program at Rockefeller. Water has a high dielectric constant ($D = 78.35$); most organic liquids have very much lower constants. Guaiacol ($o$-CH$_3$O·C$_6$H$_4$·OH) has a dielectric constant of 11.8; for water-saturated guaiacol, $D = 14.3$. Shedlovsky and Uhlig (1934) measured the conductance in guaiacol and in water-saturated guaiacol of the sodium and potassium salts of guaiacol (which show typical strong electrolyte behavior in
water). The conductance curves closely resembled those of weak electrolytes in water, and could be reproduced by equation (15); the only conclusion possible was that part of the salts \((\text{Na}^+ \cdot \text{Ge}^-\) and \(\text{K}^+ \cdot \text{Ge}^-\)) in solution were non-conducting. No neutral molecule can form from alkali cation and guaiacolate anion; instead, the non-conducting species consisted of ion pairs, anion and cation held together by the electrostatic force between ions of opposite charge, which is about seven times as great in guaiacol as in water. (According to Coulomb's law, the force varies inversely as \(D\).) The dissociation constant for the ion pair \(\text{Na}^+ \cdot \text{Ge}^-\) in wet guaiacol was found to be \(4.3 \times 10^{-5}\), about a quarter of that of acetic acid in water. These results showed that the concentration of free ions in organic media of low dielectric constant is much less than the stoichiometric concentration of salt; one infers that most of the alkali ions in biological membranes are paired with the anionic sites in proteins and nucleic acids. The dissociation of carboxylic acids is also strongly dependent on the dielectric constant of the medium, as was shown by a comprehensive study of acetic acid in water-alcohol mixtures (water-methanol, Shedlovsky and Kay, 1956; water-ethanol, Spivey and Shedlovsky, 1967; water-propanol, Goffredi and Shedlovsky, 1967). It was shown (1962) that the dissociation constant of acetic acid in the mixtures is controlled by a set of simultaneous competing reactions,

\[
\text{HA} + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{O} \cdot \text{HA} \rightleftharpoons \text{H}_3\text{O}^+ \cdot \text{A}^- \rightleftharpoons \text{H}_3\text{O}^+ + \text{A}^- \quad (18)
\]

\[
\text{HA} + \text{ROH} \rightleftharpoons \text{ROH} \cdot \text{HA} \rightleftharpoons \text{RH}_2\text{O}^+ \cdot \text{A}^- \rightleftharpoons \text{RH}_2\text{O}^+ + \text{A}^- , \quad (19)
\]

where \(\text{A}\) denotes the acetyl group \((\text{CH}_3\text{CO}_2)\) and \(\text{R}\) the alkyl group of the alcohol. A (neutral) molecule of acetic acid is solvated by a molecule of water or alcohol; by electron rearrangement, an ion pair forms, and then the latter dissociates
into free cation and acetate ion. The numerical values of the equilibrium constants that describe reaction (19) are quite different, depending on whether R is methyl, ethyl, or propyl, and therefore, the overall dissociation constant

\[ K = \frac{[A^-][H_3O^+ + RH_2O^+]f^2}{[HA]} \]  

for acetic acid is solvent-dependent. These systems present a classical example of the specific nature of short-range interactions between electrolytes and solvent molecules; the specificity is reminiscent (although far from a perfect analog) of the selectivity at the active sites on enzyme molecules.

In living cells are found potential differences as high as 100 millivolts across the cell membrane; they cannot be electrostatic in nature because electric current will flow for relatively long periods of time in a circuit established between the cell fluid and the surrounding liquid. Neither can their origin be in coupled oxidation-reduction reactions such as those that generate a voltage across the two electrodes of conventional electrochemical cells, because in the latter electrons must flow, and living cells (composed of water, salts, and organic compounds) obviously lack the purely metallic components that are essential for transport of electron currents. Shedlovsky proposed that bioelectric potentials were produced by coupled acid-base reactions in which protons carry the electric current. The model was described at a symposium at the National Bureau of Standards during its Semicentennial in 1951. The first comment in the discussion that followed Shedlovsky's presentation was made by W. F. K. Wynne Jones, who said: "Mr. Chairman, I think we have listened to a very brilliant exposition of a brilliant idea, and I would only wish that Brønsted were here today to listen to Shedlovsky." The _proto_chemical cell of biochemical systems can best be explained by reviewing the _electro_chemical cell of
the inorganic world, which consists of metallic electrodes (which are reversible to electrons) immersed in electrolytic solutions. A familiar example of the latter is the cell

\[
\text{Pt}, \text{H}_2 | \text{H}_3\text{O}^+, \text{Cl}^-, \text{H}_2\text{O} | \text{AgCl}, \text{Ag}.
\]

At the anode, hydrogen is oxidized to hydrogen ions and electrons are released to flow through the load in the external metallic circuit to the cathode where they reduce silver ions to metallic silver; the current in the solution is carried by the hydrogen and chloride ions. The cell reaction is

\[
\frac{1}{2}\text{H}_2 + \text{H}_2\text{O} + \text{Ag}^+ = \text{Ag} + \text{H}_3\text{O}^+.
\]

Shedlovsky's protochemical cell consists of a glass tube, closed at the bottom by a thin glass membrane that is coated on the inside with a layer of barium laurate and lauric acid. The tube was filled with a solution of barium chloride and hydrochloric acid and dipped into a vessel containing the same solution. Silver-silver chloride electrodes were immersed in the tube and in the vessel: potentials were measured across the latter electrodes. The glass membrane and the laurate-lauric acid coating are reversible to protons (which are carried in the solution by interchange with water molecules: \( \text{H}^+ + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O} + \text{H}^+ \)). The two protodes (a term coined by Shedlovsky to contrast with "electrodes," the entrance and exit for electrons in the electrochemical cell) are electrically connected through the solutions, the silver electrodes and the measuring circuit connecting the latter. The effective cell is

\[
\text{glass}, \text{H}_2\text{O} | \text{H}_3\text{O}^+, \text{Ba}^{++}\text{Cl}^-, \text{H}_2\text{O} | \text{BaL}_2, \text{HL}
\]

where L is an abbreviation for the laurate ion. The cell reaction is
which is an acid-base reaction in the Brønsted-Lowry sense. The protodes of biochemical systems are the inner and outer surfaces of the cell membranes, which are chemically different but both reversible to protons; protons flow through the membranes much like they flow through the glass-lauroyl interface in the Shedlovsky protochemical cell.

A quotation from a paper given at a symposium sponsored by the New York Academy of Sciences in 1943 is presented as preface to a review of Shedlovsky's work on biochemical materials:

The usual operational criteria for the purity of inorganic and organic materials, which are not megamolecular as are proteins, are constancy of density, refractive index, optical rotation, melting point, boiling point, dielectric constant, electrical conductance, solubility, analytical data, etc., after redistillation, recrystallization, or preparation by different methods. Unfortunately, most of these operations are not available for proteins. These are very labile substances, and the procedures which can be used without fear of profoundly altering them are indeed limited. Also, analytical data on proteins are of relatively little use in most cases for establishing purity, and laboratory synthesis has as yet not been possible. Among the various physicochemical procedures which are applicable to the study of proteins there are a few which provide the most satisfactory criteria we have for estimating the degree of purity. These are electrophoretic analysis, observations in the analytical ultracentrifuge, and the determination of solubility curves in suitable solvents. Proteins form salts with both acids and bases, and, except at the isoelectric point, appear as ions with a net electric charge. Their electrical mobilities depend largely on the pH and on the salt composition of the solution at a fixed temperature. Two different proteins may have identical mobilities in a given solvent, but the probability of the mobilities remaining similar at other values of pH is much smaller. The ultracentrifuge determines sedimentation constants, which depend on the size and shape of the molecules. Here again, two different proteins may happen to have similar sedimentation constants under certain conditions. Determinations of solubility curves involve analogous considerations. However, the likelihood of two different substances behaving alike in all
three respects, that is, electrophoresis, sedimentation and solubility, can probably be ruled out in the present state of our knowledge.

The identification and isolation in pure form of metaken-trin, a gonadotrophic hormone, from extracts of the anterior lobe of the pituitary gland was accomplished by physico-chemical methods (*Science*, 1940; *Endocrinology*, 1942). The electrophoretic pattern of the protein solution showed three peaks, indicating the presence of three components, only one of which was found to be biologically active. By plotting mobility against pH, their isoelectric points were determined. The active component with isoelectric point at pH 7.45 was isolated by precipitating it from solution by addition of ammonium sulfate at this value of pH; it was then purified by repeatedly dissolving and reprecipitating. Purity was established by showing that the solubility was independent of the ratio of amount of solid protein to volume of saturated solution.

The Forssman antigens are defined as substances that have the common property of evoking cell hemolysis when injected into rabbits, and are widely distributed in nature. The chemical composition and the physical and immunological properties of the Forssman antigen produced by pneumococci were studied at Rockefeller (*Journal of Biological Chemistry*, 1943). The antigen (“F substance”) was found to be a lipocarbohydrate constituted from a polysaccharide moiety to which a lipid is bound in firm chemical union. The extracts from the pneumococcus cultures also contained a soluble nitrogenous dextrorotatory carbohydrate (“C-polysaccharide”); this carbohydrate was common to the four types of pneumococcus used as source of the antigen. It was possible to separate the F-substance into lipid and a carbohydrate by rather drastic treatment: the F-polysaccharide was quite similar to the C-polysaccharide in chemical composition and
properties. Both polysaccharides precipitate in C-antiserum in dilutions of 1:2 million. But the slightly greater carbon content (45.12% vs 44.01%) of the F-polysaccharide and its lower content of reducing sugars (42.8% vs 50.6%) suggested that the polysaccharide moiety of the F-substance was indeed the C-polysaccharide, but separation from the lipid involved some chemical damage to the molecule. Electrophoresis showed that the two polysaccharides really were different: the mobilities at pH = 7.85 of the C- and F-polysaccharides are $2.2 \times 10^{-5}$ and $1.7 \times 10^{-5}$ cm/sec/volt/cm, respectively. But the peaks (both ascending and descending) in the electrophoresis patterns for the F-compound were sharp and symmetrical, while the peaks for the C-compound were broad and asymmetric (especially the descending one). The latter pattern is characteristic for a mixture of polyelectrolytes distributed around an average value, while a sharp peak is obtained for substances that have a definite molecular weight. This observation confirmed the idea that the polysaccharide part of the F-substance was somewhat degraded by the separation from the lipid.

Electrophoresis was the tool used to follow the formation of proteolytic enzymes in cultures of Type A streptococcus (Journal of Experimental Medicine, 1951). The precursor of the proteinase has an isoelectric point at pH = 7.35, and the enzyme at pH = 8.42. In a buffer solution at pH = 7.35 (where the net charge on the precursor is zero), the molecules of the precursor will remain stationary in the electrophoresis cell while the enzyme, which carries a positive charge, will move in the electric field. Consequently, the rate of the reaction (precursor $\rightarrow$ enzyme) can be followed by taking samples from a reacting system, adding iodoacetic acid or ethanol as inhibitor to the sample to stop the reaction, and then running the electric current until the enzyme peak has moved away from the precursor peak. The area under the
peak is proportional to the concentration of enzyme; hence, the observer can follow the rate of the biochemical reaction.

Immunology has its origins in Jenner's observation that inoculation with vaccine obtained from the vesicles of a calf infected with vaccinia (cowpox) produced immunity to smallpox. The vaccine is chemically a most complicated mixture; identification and isolation of its components have been the research field for laboratories the world over.

In addition to the immunizing antigens in the vaccine, a variety of other antigens has been found, their presence having been indicated by the variety of antibodies found in the sera of animals following vaccination. The antigens L (heat-labile) and S (heat-stable) were studied intensively at Rockefeller; again, electrophoretic data furnished essential information that permitted isolation and purification of the antigen from the multitude of other substances in the vaccine. By separating through isodielectric precipitation a substance that gave a single peak in the electrophoresis pattern but possessed both L- and S-activities, it was found that both L- and S-immunological activities reside in a single protein molecule. The pure LS-antigen, after heating in solution at 70° for one-half hour, no longer precipitated with L-antibody but did so with S-antibody. On treatment of LS-antigen with chymotrypsin (a proteolytic enzyme), the product precipitated with L-antibody but not with S-antibody. In other words, one could selectively destroy either the L-activity or the S-activity, starting with a molecule that possessed both activities. The LS-protein, the soluble double antigen of vaccinia, is homogeneous electrophoretically and in the ultracentrifuge. It is characterized by the following properties: isoelectric point at pH = 4.8, specific volume at 4° is 0.72 cc/gm, diffusion coefficient $1.50 \times 10^{-7}$, sedimentation constant 6.35 Svedberg at 20°, molecular weight 214,000, axial ratio 1:20. These results provide a complete physicochemical description of the protein.
Theodore Shedlovsky was born in St. Petersburg (now Leningrad) on October 29, 1898. He began living in the United States in 1908, and became a citizen in 1927. He received the degree of Bachelor of Science in 1918 and the degree of Doctor of Philosophy in 1925 from the Massachusetts Institute of Technology, where he was an assistant in physical chemistry from 1918 to 1921. He joined the Rockefeller Institute for Medical Research (which became The Rockefeller University in 1965) as a research assistant in 1927 and spent the rest of his life at Rockefeller, holding posts of research associate (1928–1944), associate member (1944–1956), and member and professor (1956–1969). He became Professor Emeritus in 1969 but did not retire from activity at Rockefeller until about two years before his death. In recognition of his many services to science and to Rockefeller, the University conferred on him an honorary degree of Doctor of Science in 1975.

Dr. Shedlovsky was elected to membership in the National Academy of Sciences in 1953. He was also a member of the New York Academy of Sciences (vice-president, 1942–1960), the American Chemical Society, the Harvey Society, the Electrochemical Society, the Biophysical Society, and the American Association for the Advancement of Science.

Shedlovsky is survived by his first wife (née Gladys Lillian Danielson) and their son Richard, who is executive director of the Hebrew Hospital for Chronic Sick (Bronx, New York); his widow (née Beatrice Paul), their daughter Alexandra Shedlovsky Dove, who is a research biochemist at the University of Wisconsin, and their son Julian, who is an administrative officer at the National Center for Atmospheric Research at Boulder, Colorado; and his brother, Dr. Leo Shedlovsky, who is also a physical chemist, now retired. There are eight grandchildren: Richard’s Joan and Ellen; Alexandra’s William, Patrick, and Susanne; and Julian’s Erica, Paul, and Sarah.
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