but this must be recognized and made applicable to important relevant problems. This attractiveness has approximately doubled the proportion of U.S. Ph.D.'s in analytical chemistry over the last 20 years, with demand still exceeding supply.

High data rates are a compelling attraction of modern instrumentation. However, we analytical chemists can be overly enamored with the acquisition of data itself. Quoting the philosopher deBono, "data is not information until it has been processed into an idea". A real solution here has been the computer revolution. The gas chromatograph/mass spectrometer produces megabit/second data; even with a compound eluted from the GC every few seconds, probability-based matching against 140 000 reference mass spectra is fast enough for real-time identifications.[5] Similarly, obtaining even more detailed structural information from even larger molecules by multidimensional NMR requires further "automation of the spectral analysis".[6] Within such a broadened definition, analytical chemistry is an important part of many *Accounts* articles of 1988 and 1989.[6,7]

I do not ask that individual experts in such methodologies categorize themselves as analytical chemists. However, the separate discipline of analytical chemistry deserves more consideration for the vital role it can play. Its unusual diversity puts an even greater value on finding common interests, discussing alternative approaches to analytical problems, and utilizing new developments in theory, instrumentation, electronics, and computers. A disproportionate part of the effort for a specific research problem can involve developing special analytical tools; a much smaller additional effort could make these suitable and appealing for important research of others. Analytical chemistry offers a forum for encouraging and evaluating both basic and applied research critical to the acquisition and utilization of chemical information, as I hope is reflected in the pages of this journal.[3,4,6,7]

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ARTICLES

High-Speed Cyclic Voltammetry

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The time scale of voltammetric measurements has been decreased by several orders of magnitude in the last decade. Cyclic voltammograms recorded at scan rates in the range of 10^6 V/s have been reported.[1,2] At these scan rates, transient electrogenerated species with a lifetime of ≈ 20 ns can be characterized. Thus, cyclic voltammetry now can be used on a time scale that is unprecedented for electrochemical methods. This reduction in time scale presents new opportunities for applications of voltammetry in the characterization of solution redox behavior as well as chemical analysis.

Cyclic voltammetry is perhaps most widely used by chemists as a method to determine the standard reduction potential of a redox couple, $E°$. Normally this is done by recording the position of the peaks of the voltammetric waves of the voltammograms and using

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this information to calculate the relevant $E°$'s. However, under conditions where the current is a result of accompanying chemical reactions as well as the basic electrochemical process, the position of the voltammetric wave on the potential axis is a function of all of these processes. Thus, it becomes necessary to make measurements on a rapid time scale so that the occurrence of any accompanying chemical reactions is outrun. This can be done more readily now that shorter time scales can be attained.

Cyclic voltammetry is also useful to characterize a variety of other processes. The rates and mechanism of chemical reactions that accompany the heterogeneous electron transfer can be determined. Voltammograms contain information concerning the rate of heterogeneous electron transfer between the solution species and the electrode surface. Voltammetry is also useful in chemical analysis. In all of these applications, the use of these new approaches permits exploration of new, much shorter time domains.

The reduction in time scale of voltammetric measurements has been made possible by the use of electrodes of much smaller size than conventional electrodes.[3,4] They are referred to as microvoltammetric electrodes or ultramicroelectrodes and have dimensions of micrometers or less. The small currents associated with these electrodes result in an electrochemical cell that can respond in a much more rapid fashion to a potential change applied to the electrode. Before the advent of microvoltammetric electrodes, measurements with cyclic voltammetry were typically limited to the millisecond time scale.[5] Today, undistorted measurements can be made on a microsecond time scale in typical solutions used for voltammetry. In addition, since the sources of distortion at microvoltammetric electrodes are well understood, these can be accounted for to permit events in the nanosecond range to be characterized.

Cyclic Voltammetry of 9-Bromoanthracene

An illustration of the large amount of information that can be obtained by high-speed cyclic voltammetry is given by our recent reports of the reduction of various aryl halides. In general, halogenated organic compounds form the corresponding hydrocarbons when electroreduced in an overall process that involves two electrons.[6] There has been considerable interest in the use of high-speed voltammetry to determine the reaction mechanism whereby this occurs.[1,2,7] Some aryl halides have been shown to undergo electroreduction followed by a subsequent rate-determining step. In contrast, alkyl halides appear to undergo electroreduction and bond cleavage in a concerted process. However, because of the temporal limitations of conventional cyclic voltammetry, the possibility exists that a compound that follows a two-step process could be misassigned as a concerted process since the intermediate radical anion would be too short-lived for observation.

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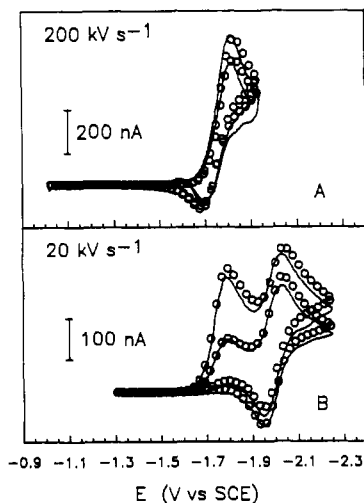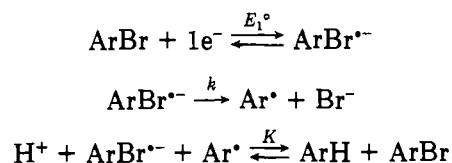(7) Wipf, D. O.; Wightman, R. M. *J. Phys. Chem.* 1989, *93*, 4286–4291.

Figure 1. Reduction of 4.8 mM 9-bromoanthracene at a 3-μm-radius gold disk electrode in acetonitrile containing 0.6 M tetraethylammonium perchlorate. Solid lines: background-subtracted cyclic voltammograms at 20 000 V s^{-1} (A) and 200 000 V s^{-1} (B). Open circles: digital simulation of the voltammograms for the proposed mechanism with $k = 6 \times 10^5$ s^{-1}. Reprinted with permission from ref 7. Copyright 1989 American Chemical Society.

The electroreduction of 9-bromoanthracene provides an example of such a short-lived intemediate. This compound was thought to be reduced to its radical anion, with subsequent halide-bond cleavage, by analogy with other, more stable compounds of similar structure, and because of experimental results from the indirect method of redox catalysis.[6] However, the use of high-speed voltammetry gives direct evidence for the presence of an intermediate (Figure 1). At modest scan rates (Figure 1B), the reduction occurs as a two-electron process, and no reverse wave is seen, indicating that the radical anion, if it exists, has decomposed during the time of the scan. At more negative potentials, a reduction wave is observed for the reduction of anthracene formed as a result of the overall reaction. At very rapid scan rates (Figure 1A), a reverse wave associated with initial reduction becomes apparent and the number of electrons per mole (n) involved in the initial reduction decreases from 2 to 1; both of these features are those expected from the formation of the 9-bromoanthracene radical anion. Data taken at various scan rates corresponding to a time scale of 4 orders of magnitude allow the lifetime of the radical anion to be determined as 6×10^5 s^{-1}. This data provides clear evidence that the reaction is not a concerted process.

Superimposed on the cyclic voltammograms are simulated voltammograms, which were computed on the basis of a mechanism involving the following major pathways:

$$\text{ArBr} + 1e^- \underset{}{\overset{E_1°}{\rightleftharpoons}} \text{ArBr}^{\bullet-}$$

$$\text{ArBr}^{\bullet-} \overset{k}{\longrightarrow} \text{Ar}^{\bullet} + \text{Br}^-$$

$$\text{H}^+ + \text{ArBr}^{\bullet-} + \text{Ar}^{\bullet} \overset{K}{\rightleftharpoons} \text{ArH} + \text{ArBr}$$

Here ArBr represents bromoanthracene and ArH represents anthracene. The agreement of the simulated and measured data strongly support this assignment. However, the fitting of the data requires values for all of the kinetic and thermodynamic quantities. This can be done by the use of data for various time domains.

For example, values of n and the diffusion coefficient are most easily determined from the peak current at slow scan rates. The $E_1°$ value and the rate of heterogeneous electron transfer are readily obtained at very short time scales where the radical anion is stable. The transition of the wave height from two- to one-electron behavior with increasing rate constant is used to provide the value of the rate constant. The value of K is set so that a complete reaction is assumed consistent with the strong oxidizing power expected for Ar·.

Advantages of Very Small Electrodes

The high-speed measurements described above are obtained more easily with microvoltammetric electrodes than with conventional electrodes because the impedance of electrochemical cells containing microelectrodes is much smaller. The combined presence of the double layer at the working electrode interface, with its associated capacitance, and the finite resistance of the solution between the working and counter electrode means that electrochemical cells act as low-pass filters with respect to the applied voltage.[3] Distortion of the applied voltage results in a distorted voltammogram. However, as the electrode dimensions are reduced, the equivalent "time constant" is also reduced, meaning that higher rates of scan can be achieved without distortion of the voltammogram. For the specific case of a disk-shaped electrode, the reduction in time constant is linearly dependent on the radius of the electrode.[4] An additional source of distortion arises from the current that flows through the cell. This generates a potential that opposes the applied potential. However, this "ohmic drop" is also proportional to the electrode radius. Thus, both of the major sources of distortion for high-speed measurements are made smaller by a reduction in electrode size.[8,9]

The small value of the time constant of electrochemical cells containing very small electrodes is clearly indicated by the work of McCreery and co-workers.[10] They have used potential steps at micrometer-sized electrodes to electrogenerate substances in the working electrode interfacial region. Rather than monitoring of the current, which has a large contribution from double-layer charging processes at short time scales, the concentration profile of the electrogenerated species is monitored by absorption spectrometry. The measured data agree with theory at times as short as 150 ns at microdisk electrodes, demonstrating that the lag of the applied potential is small. Such spectroelectrochemical experiments can also be used to measure very fast reactions of electrogenerated species in the diffusion-layer region. For example, a rate constant of 6.2×10^7 M^{-1} s^{-1} has been reported for the reduction of chlorpromazine radical cation by dopamine at a pH of 6.8.

Figure 2 illustrates the effect of electrode radius on the ohmic drop observed in cyclic voltammograms. In this example, the data was acquired from chlorobenzene solutions under conditions where the effect of the time constant of the cell is negligible. The specific resistance
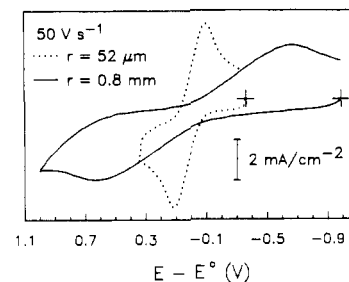

Figure 2. Cyclic voltammograms of 1.1 mM ferrocene in chlorobenzene with 0.5 M tetra-*n*-hexylammonium perchlorate supporting electrolyte at 0.8-mm-radius (solid line) and 52-μm-radius (dotted line) gold disk electrodes recorded at 50 V s^{-1}. The current scale is normalized to the electrode area.

of this solution is approximately 300 times greater than that of typically used aqueous solutions. Note that the peak position in the voltammogram recorded at the larger electrode is shifted by over 600 mV from its true position as a result of ohmic drop. The ohmic drop sets an upper sweep-rate limit of ~1 V s^{-1} for this solution at the electrode of conventional size, whereas this limit can be increased by the use of smaller electrodes.[11]

This example also illustrates that the term "high speed" is a relative one. Measurements with ultramicroelectrodes can always be made at faster time scales than measurements with electrodes of conventional size. The solution properties that determine the time constant and ohmic drop, however, will dictate the upper useful scan rate. Because these sources of distortion are well understood at microelectrodes, the distortion can be predicted and, in many cases, removed from the curve.[1] The amplifier band-pass can also distort the cyclic voltammograms. However, instruments with a band-pass of greater than 1 MHz (equivalent time constant of 160 ns) have been constructed by several groups[1,3,12] and allow data to be collected in the kV s^{-1} range without distortion.

In addition to an upper scan-rate limit, a lower scan-rate limit exists as well. At long time scales (slow scan rates), mass transport to very small electrodes can occur by convergent[3,4] as well as linear diffusion, which can greatly alter the shape of the voltammogram. Although the case of convergent diffusion can be mathematically handled, the analysis is difficult and time-consuming.[13] In contrast, the theoretical responses for cyclic voltammetry under linear-diffusion conditions exist for a wide number of cases and modification of the existing solutions is straightforward.

Alternative Ways To Achieve High-Speed Voltammetry

Several ways to improve the response time of electrochemical cells were explored prior to microelectrodes. The classical approach has been to lower the apparent solution resistance with the use of a three-electrode cell and potentiostat.[5] In this arrangement, the reference electrode senses the potential of the working electrode and provides a correction signal via the potentiostat to compensate for the ohmic drop. Current flows to the

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working electrode from a large auxiliary electrode under potentiostatic control. The reference electrode is usually placed in a thin probe, a Luggin–Haber capillary, which can be positioned very close to the electrode, which minimizes the effect of the solution resistance. In the late 1960s, Perone[14] was able to record voltammograms at scan rates in excess of 2000 V s^{-1} in aqueous electrolytes with an electrode of 500-μm radius and a carefully positioned capillary. Even faster scan rates were reported with a smaller, less well defined mercury drop.

Despite its utility, the Luggin–Haber is difficult to use reproducibly because it must be placed very close to the working electrode to achieve resistance compensation. If it is too close, it can distort the potential and current distribution at the working electrode.[15] An alternate approach is to electronically achieve ohmic compensation.[16] This approach has been used to achieve scan rates of over 5000 V^{-1} with electrodes of conventional size.[17] However, this method can lead to oscillations of the potentiostat circuit because it employs positive feedback.[18] An alternate instrumental approach was to inject charge rapidly into the double layer with a coulostatic apparatus.[19] It is likely that these methods may also be useful with microelectrodes as well. Recently, ohmic compensation has been used at microelectrodes.[20]

Measurement of Heterogeneous Kinetics with High–Speed Voltammetry

When voltammetry is used at short time scales under conditions where undistorted voltammograms are obtained, the most predominant feature that is observed with chemically stable redox couples is the effect of finite electron-transfer kinetics. This manifests itself in cyclic voltammetry in the form of an increased separation in the position of the forward and reverse waves over the 60/n mV expected for an electrochemically reversible system.[5] However, couples with very large rate constants, which could serve as test systems of reversible behavior at short time scales, are not known. However, a few systems have been measured with electrodes of conventional size (and thus the millisecond time domain) and reported to have heterogeneous rate constants of approximately 1 cm s^{-1}. For example, the heterogeneous rate constants measured for benzoquinone and naphthoquinone in acetonitrile are modest at gold electrodes ($k°$ = 0.4 and 0.8 cm s^{-1}, respectively), and thus their rates can be determined by cyclic voltammetry with both disks of 5-μm radius and electrodes of conventional size.[1] Good agreement was found with the two methods. The heterogeneous rate constants for the reduction of anthracene with microelectrodes in dimethylformamide[21] and hexaammineruthenium(III)
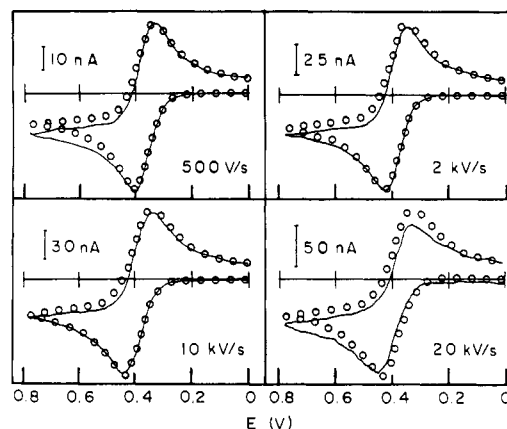

Figure 3. Voltammograms with background current subtracted for the oxidation of 2 mM ferrocene in acetonitrile containing 0.6 M tetraethylammonium perchlorate obtained at a 5-μm-radius gold disk electrode. Solid lines: experimental data. Open circles: simulated data for $k°$ = 3.1 cm s^{-1} and α = 0.5. Reprinted with permission from ref 9. Copyright 1988 American Chemical Society.

in aqueous solution[9] are within the range reported when measured at larger electrodes.[22,23]

The distortion at high sweep rates should not prevent the measurement of heterogeneous rate constants with values as great as 5 cm s^{-1}. Thus, the heterogeneous rate constants for a number of other compounds expected to exhibit high rates, and thought to proceed by an outer-sphere mechanism of electron transfer, have been characterized. These include anthraquinone ($k°$ = 1.8 s^{-1}), ferrocene ($k°$ = 3.1 cm s^{-1}), and Ru(bpy)$_3$$^{2+}$ (bpy = 2,2'-bipyridine) ($k°$ = 2.5 cm s^{-1}) on gold microdisk electrodes in acetonitrile.[3,9] In general, the rate constants are found to be smaller at platinum microvoltammetric electrodes,[3,9,24] illustrating the nonpassive role of the electrode material in such measurements. However, with both electrode materials, the rate constants are found to be larger than those measured at conventionally sized electrodes. The larger values are more likely correct because of the difficulties in the measurement of rapid heterogeneous kinetics at conventional electrodes. Rate constants reported for ferrocene oxidation at large electrodes are particularly scattered, with values ranging over 2 orders of magnitude. The largest values are found with microelectrodes, and the data fit well over a broad range of scan rates (Figure 3).

Determination of $E°$'s for Unstable Species

As indicated in the introduction, high-speed voltammetry is particularly suited to the determination of $E°$'s of chemically unstable couples and for studying the chemistry of such couples. Scan rates greater than 1000 V s^{-1} were used to obtain the reversible reduction potential of the diphenylanthracene cation/dication couple.[25] Through such measurements, the equilibrium constant for the disproportionation of the radical cation of this compound was determined and found to be

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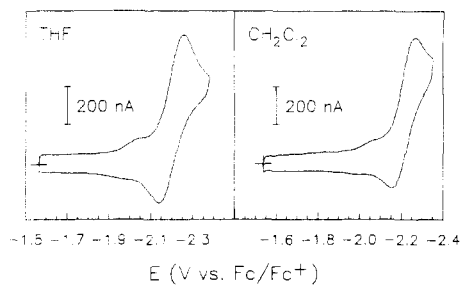(25) Howell, J. O.; Wightman, R. M. *J. Phys. Chem.* **1984**, *88*, 3915–3918.

Figure 4. Voltammograms of 1 mM 9-chloroanthracene in tetrahydrofuran and methylene chloride with 0.5 M tetra-n-butylammonium perchlorate at a 52-μm-radius gold disk electrode recorded at 63.1 V s^{-1}. The difference in the size of the reverse wave for 9-chloroanthracene in the two solvents indicates a 5-fold difference in the lifetime of the 9-chloroanthracene radical anion.

solvent dependent. Significantly larger values were found in dimethoxyethane than methylene chloride or acetonitrile, presumably because of the greater solvation of the dication in the former solvent. A large solvent effect has also been found in the reduction of quinones at high pH in protic solvents with high-speed voltammetry.[26] The equilibrium constant for the disproportionation reaction of the quinone radical anion was shown to correlate with the ability of the solvent to form hydrogen bonds.

The reversible potentials for the oxidation of 24 methyl-substituted benzenes in trifluoroacetic acid have been measured with high-speed voltammetry.[27] These results, which could not be obtained with conventional electrochemical methods, were correlated with the gas-phase vertical ionization potentials. An excellent correlation was found but with a slope less than unity. This may reflect the stabilization of the radicals by solvation. High-speed cyclic voltammetry has also been used to observe the two-electron-oxidation product of ascorbic acid at a mercury electrode.[28] In aqueous solution (pH 7.0), the oxidized form of ascorbate has a lifetime of 0.5 ms as a result of a hydration reaction and, thus, cannot be observed in voltammograms obtained at conventional electrodes. Millisecond-time-scale conformation changes of the 1,1'-bianthrone radical anion in dimethylformamide have also been characterized with high-speed voltammetry.[29] In this example, the added time resolution provided by the microvoltammetric electrodes allowed the reaction to be probed at elevated temperatures.

Voltammetry without distortion can be achieved with ultramicroelectrodes in solvents with low concentrations of supporting electrolyte or in solvents with a low dielectric constant at higher scan rates than with conventional electrodes. The specific conductivity of dimethoxyethane containing 0.5 M tetrabutylammonium perchlorate is approximately one-tenth that of the acetonitrile solution described earlier, while the capacitance is unchanged.[11] Thus, the upper scan-rate limit in this solution that avoids the effects of the cell time constant is lower by a factor of 10, but relatively fast scans can still be used to obtain quantitative information.[25]

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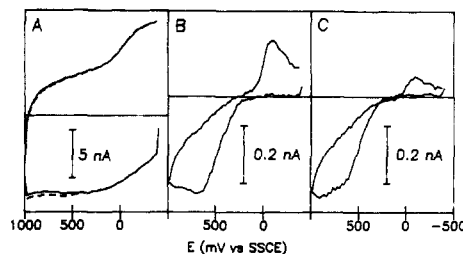
Figure 5. Voltammograms of norepinephrine and epinephrine recorded at a 6-μm-radius carbon-fiber electrode at 300 V s^{-1} in aqueous solution, pH 7.4. (A) Background voltammogram and voltammogram with electroactive species present. (B) Subtracted voltammogram of norepinephrine. (C) Subtracted voltammogram of epinephrine.

In some circumstances it becomes advantageous to use relatively large microelectrodes (50-μm radius). Although the upper scan-rate limit is compromised, the use of larger electrodes enables voltammograms under conditions of linear diffusion to be obtained at lower scan rates. This has been used to determine $E°$'s and lifetimes of 9-chloroanthracene (Figure 4) in a variety of solvents.[11] As this example illustrates, the size of the electrode should be selected to match the solution conditions and the sweep rates that are desired. Low temperatures are often used in voltammetry to stabilize transient intermediates. Cyclic voltammetry at ultramicroelectrodes at scan rates of thousands of volts per second have been demonstrated to be possible in such low-temperature solutions, providing additional information.[30]

Analytical Applications of High-Speed Voltammetry

Cyclic voltammetry at microvoltammetric electrodes is also used in analytical applications. In this case, the use of high speed is advantageous when the analyte is rapidly changing in concentration. A voltammogram recorded at 300 V s^{-1} takes less than 10 ms to acquire and provides an identifier of the compound which changed in concentration between successive scans. This approach has been highly successful in the detection of the dynamics of the catecholamine dopamine in the brain of living animals.[31] Dopamine is a neurotransmitter, and its concentration in the extracellular fluid of the brain can fluctuate rapidly. Thus, this type of rapid detection scheme is required.

While rapid concentration changes can be measured in this way, the background current arising from charging the double layer and other surface processes may obscure the faradaic current, the current arising from species diffusing to the electrode. This is because the current from surface-associated processes increases linearly with scan rate, while the current arising from diffusing species increases with the square root of the scan rate. The large amplitude of the charging current reduces the information content of the voltammogram because it occupies a significant portion of the available resolution in a digitized representation of the data.[32] A dummy cell, comprising components that approximate the cell impedance, can be used to remove the signal. A current of equal magnitude but opposite sign to the

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cell background current can be generated through this circuit and directly subtracted from the cell current. Since a precise match of the dummy-cell characteristics to those of the electrochemical cell is difficult, this method is usually used with digital subtraction of the background signal. A cyclic voltammogram recorded without the faradaic component present is subtracted from a voltammogram recorded in a solution that contains the species of interest (as illustrated in Figure 5, parts A and B). This removes the background signal and any mismatch of the dummy cell and the electrochemical cell. In addition, several voltammograms are collected and averaged to further increase the dynamic range as well as the signal-to-noise ratio.[33]

The short time during which electrolysis occurs during high-speed voltammetry can also be advantageous. For example, the oxidation of 5-hydroxytryptamine, also a neutrotransmitter, results in polymeric products which can form an insulating film on the electrode surface. When a rapid scan rate is employed, the amount of oxidized material generated is small, and passivation of the electrode response is avoided.[33] The use of high scan rates also allows the discrimination between different compounds that have similar $E°$'s but differ in their rates of chemical reaction after electron transfer. An example we have recently been investigating is to distinguish between epinephrine and norepinephrine, two compounds of biological importance which differ only in the presence of a methyl group on the side chain of the basic catecholamine structure. When these compounds are oxidized, the side-chain amine can add to the ring, resulting in a disappearance of the o-quinone form. The rate of the intracyclization reaction is faster for epinephrine. This is apparent in the shapes of the voltammograms, which permit distinction of the two species (Figure 5, parts B and C), whereas at slower scan rates, the cyclization is observed to be complete for both compounds.

Pushing the Limits of High-Speed Voltammetry

Many of the results with microvoltammetric electrodes described earlier in this Account were obtained under conditions where the effects of ohmic drop and cell time constant were sufficiently small that distortion was not an issue. However, at very high scan rates, distortion of the faradaic signal occurs even with very small electrodes. Voltammograms can be recorded at very high speeds quite easily; however, the central question is the method of extracting quantitative information from the distortion.

One significant problem is the distortion caused by the current amplifier. Since the currents tend to be small with microvoltammetric electrodes, low-noise, high-bandwidth amplifiers are required. Assuming that the amplifier characteristics are equivalent to those of a first-order low-pass filter, then an amplifier time constant can be defined at which a reversible cyclic voltammetric wave will suffer minimum distortion. Such calculations show that if the product of the time constant times the scan rate is equal to 4 mV for a one-electron process, the peak potential for a reversible voltammogram will be shifted by 4 mV, a figure we have taken as a maximum allowable distortion.[9] Thus, if an
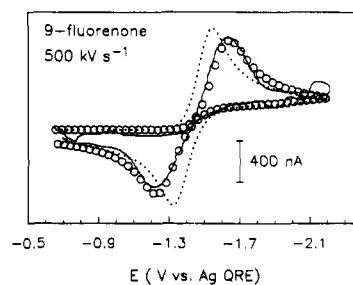

Figure 6. Background-subtracted cyclic voltammogram recorded at 500 000 V s^{-1} of 5.6 mM 9-fluorenone in 0.6 M tetraethylammonium perchlorate/acetonitrile at a 3-μm-radius gold disk electrode. Solid line: experimental voltammogram after correction for instrument distortion. Open circles: simulation accounting for faradaic process, ohmic drop, and cell time constant. Dotted line: simulation with only the faradaic part considered. Reprinted with permission from ref 1. Copyright 1988 American Chemical Society.

amplifier has a time constant of 100 ns, the maximum scan rate is about 40 000 V s^{-1}. Saveant and co-workers have used a less conservative value for the upper scan-rate limit for instrumental distortion.[12,21] When scan rates are used above the limit imposed by the amplifiers, distortion can be removed by deconvolution.[1,34] With this technique, we were able to obtain cyclic voltammograms at scan rates of 10^6 V s^{-1} from a current transducer with a time constant of 130 ns. Of course, the best solution is to build an amplifier system that is sufficiently fast to record the events of interest in an undistorted way. An instrument with a 20-ns rise time for cyclic voltammetry and chronoamperometry has been described.[12]

The distortion introduced by the cell impedance and instrument response characteristics at very fast scan rates should be considered in quantitative evaluation of the results obtained. Approximate lifetimes of unstable species generated voltammetrically have been obtained directly from the data.[35] However, more sophisticated analysis methods have been used. One approach is to simulate the entire recorded curve with the use of a semianalytical equation which accounts for the interaction between the faradaic and charging current.[36] Alternatively, the potential at the working electrode can be deduced from the observed experimental current and cell resistance. This potential is then used in simulations of the experimental current. This potential axis has also been used for the analysis of the semiintegrated form of the faradaic current.[21] Our aproach has been to simulate the voltammograms which have been background subtracted.[1] Simulated and experimental examples are shown in Figure 6. The data simulated for the faradaic current alone dramatically indicate the effect of the distortion that can occur at very high rates of scan. However, once the distortion is removed or accounted for, very fast cyclic voltammetry measurements can readily be used for the determination of rate constants for chemical reactions of electrogenerated compounds.

In conclusion, the decrease in ohmic drop and cell time constant associated with electrodes of small radius allows the acquisition of cyclic voltammetric data at

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scan rates many orders of magnitude greater than was previously possible. The advantages of the use of high-speed electrochemistry at ultramicroelectrodes for the examination of heterogeneous and homogeneous kinetic phenomena have been established. Particularly advantageous is the ability to make voltammetric measurements at high speeds in solvents that are too resistive for use at large electrodes, thus opening new areas of study. The use of even smaller electrodes in the future should allow shorter time scales to be ex-

plored.[37] Currently, the limitation to the use of even faster scan rates, or shorter time scales, is the lack of current transducers with sufficient sensitivity and bandwidth to allow the use of smaller electrodes.

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Biosynthesis of Non-Head-to-Tail Terpenes. Formation of 1'–1 and 1'–3 Linkages

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When Ruzicka proposed the biogenetic isoprene rule in 1922, he recognized that individual isoprene units can be joined to one another at different positions.[1-4] The five-carbon segments are attached by a "regular" or head-to-tail fusion in the vast majority of cases, and numerous naturally occurring terpenes have been identified that contain this linkage. Isoprene units joined by "irregular" or non-head-to-tail bonds are encountered less frequently. Prior to the use of radioisotopes to establish biosynthetic pathways, the most prominent non-head-to-tail isoprenes were carotenes, although as early as 1934 Robinson[5] had pointed out a structural resemblance between sterols, as typified by cholesterol, and squalene. Similar analogies were also drawn between squalene and polycyclic triterpenes.[2-4] In 1952 Bloch and co-workers established that squalene was an intermediate in cholesterol biosynthesis by incorporation experiments with radiolabeled acetate.[6] Subsequent work from a number of laboratories has demonstrated that non-head-to-tail compounds are important intermediates in several branches of the isoprene biosynthetic pathway. This Account briefly reviews naturally occurring non-head-to-tail linkages and addresses mechanistic questions concerning biosynthesis of isoprenes with 1'–1 and 1'–3 bonds.

Structure of Non-Head-to-Tail Isoprenes. Only a limited number of fusions between isoprene units are found in nature. These are illustrated in Scheme I. Inspection of the structures reveals a common motif. If the isoprene units are numbered to reflect the original location of the diphosphate moiety in dimethylallyl diphosphate or isopentenyl diphosphate, the five-carbon building blocks for all higher isoprenes, C(1') of one

Scheme I
Linkages for Non-Head-to-Tail Isoprenes
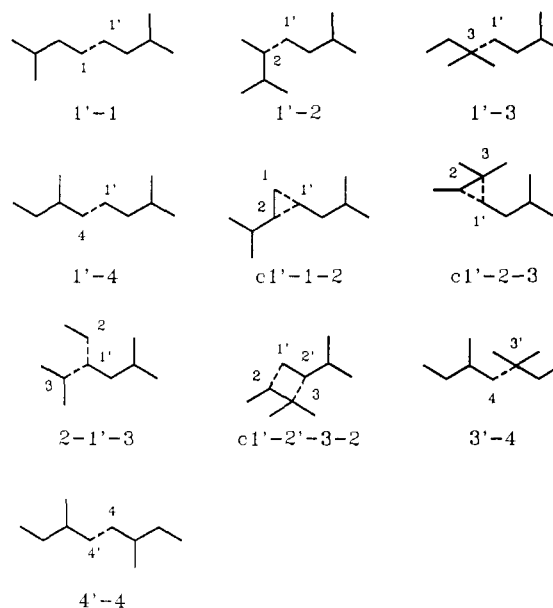
isoprene residue is usually attached to or embedded in the other. The only exceptions are the 3'–4 attachment found in artemone[7] and the 4'–4 fusion in the isoprene residues of archaebacterial tetraethers.[8] As previously noted, the 1'–4 (heat-to-tail) linkage is most common. It is generated during the fundamental polymerization reaction of isoprene metabolism where successive

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