Voltammetry with Microscopic Electrodes in New Domains

R. MARK WIGHTMAN

Voltammetric electrodes of microscopic dimension, termed ultramicroelectrodes, can be used to make measurements that are difficult or impossible with conventional electrochemical techniques. Measurements of chemical concentration can be made with these electrodes on a microsecond time scale and with micrometer spatial resolution. In addition, measurements can be made in highly resistive solutions.

When the size of voltammetric electrodes is decreased from the millimeter to the micrometer scale, many changes occur in their voltammetric behavior. These changes lead to dramatic improvements in the quality of electrochemical data and facilitate several types of experiments that were previously impossible. The major areas of improvement include increased temporal resolution, decreased sensitivity to the effects of solution resistance, and the ability to make spatially resolved chemical measurements. In the past few years, these unique features of ultramicroelectrodes have been investigated in some detail and exploited in a variety of chemical applications. In this article the properties of ultramicroelectrodes that are advantageous in voltammetric measurements will be described and some of their chemical applications will be summarized to illustrate the new possibilities that exist.

Although the advantageous properties of very small electrodes were recognized for many years, research in this area did not become active until the late 1970s. The advances made in the field of electronics, especially in the measurement of very small currents, and the advent of microstructural materials provided the tools that were necessary to build and use electrodes of small dimensions. Fleischmann and co-workers at the University of Southampton initiated much of this activity with an interest in understanding electrode mechanisms under conditions of high current density (*1, 2*). At the same time, miniature electrodes were being developed for in vivo use (*3, 4*). By 1981 it was clear that many new areas that were inaccessible to electrodes of larger size could be explored with very small electrodes, and an early review summarizes many of these expectations (*5*). Since that review appeared, significant advances have been made in the exploitation of these small electrodes.

Several characteristics give ultramicroelectrodes their advantageous properties. Because of their small area, their double layer capacitance is reduced relative to that of electrodes of conventional size. This allows the electrode potential to be changed rapidly, which permits voltammetric measurements to be made on a microsecond time scale (*6–8*). Since the electrolysis current for a compound is proportional to the electrode dimensions, this parameter is also smaller at ultramicroelectrodes. This is advantageous since measurements can be made in highly resistive domains. In fact, amperometric measurements have been made in the outlet of a gas chromatograph, with the current presumably carried by a slightly conductive layer between two adjacent microelectrodes. (*9*). In addition, voltammetry at ultramicroelectrodes is often a time-independent process, in contrast to voltammetry at larger electrodes, and this characteristic is useful in sensor applications (*10*).

Construction of Ultramicroelectrodes

The geometries of several different types of microelectrodes are shown in Fig. 1. The first microelectrodes for voltammetric applications were constructed with fine metal wires or carbon fibers (*3, 10, 11*). These can be sealed in tapered glass capillaries in much the same way that electrodes for physiological applications are prepared. Carbon fibers can be obtained with radii of 5 μm, and fine wires of gold or platinum can be obtained with a range of radii from 0.3 to 50 μm. Disk electrodes are prepared by cutting the fiber or wire flush with the insulator surface. Cylindrical electrodes can be

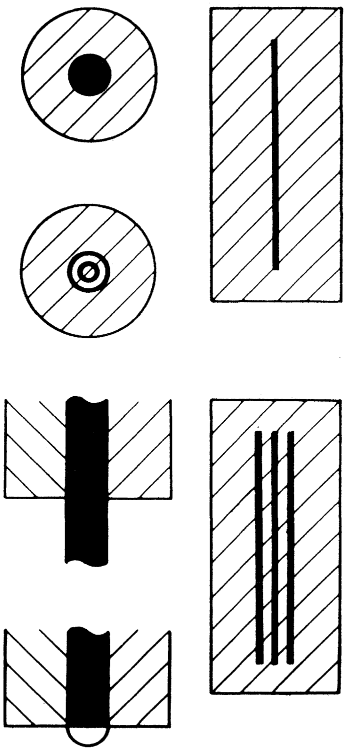


Fig. 1. Examples of the geometries of ultramicroelectrodes.

The author is a professor of chemistry at Indiana University, Bloomington, IN 47405.

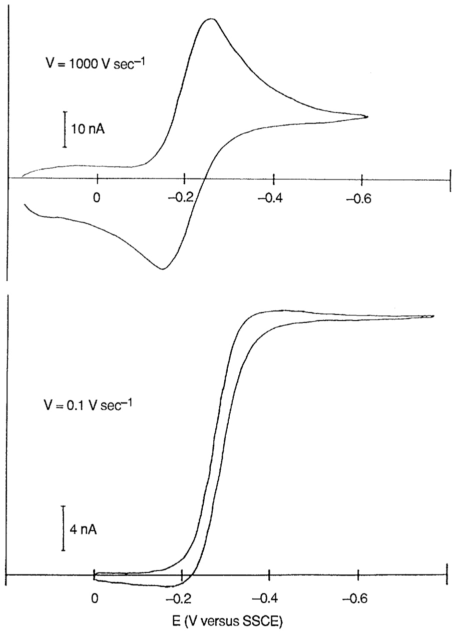


Fig. 2. Cyclic voltammograms for the reduction of 1 m*M* $Ru(NH_3)_6^{3+}$ in an aqueous 0.1*M* sodium trifluoroacetate solution at a hemispherical mercury ultramicroelectrode ($r_0 = 5.5$ μm) at slow and fast scan rates. SSCE, saturated sodium calomel electrode.

prepared by allowing a portion of the wire or fiber to protrude from the insulator (*12*). The cylindrical geometry has the advantage of larger currents, facilitating noise-free detection, but these electrodes tend to be mechanically frail and cannot be easily polished to obtain a fresh surface. Mercury ultramicroelectrodes can be prepared by electrodeposition of mercury onto microdisks or cylinders. When the deposited mercury completely covers the substrate, all of the advantages normally associated with mercury voltammetric electrodes are obtained (*13*). Arrays of platinum disks have been prepared by electrodeposition of platinum into the pores of a polycarbonate membrane (*14*).

Electrodes with a band geometry are attractive because they can be fabricated on the nanometer scale in one dimension. Although the current at a single disk of such dimensions would be immeasurably small, the magnitude of the current at a band electrode is determined by its length and can be readily measured. One approach to their fabrication is to sandwich thin metal films between glass or epoxy insulators (*15, 16*). Bands with a smallest dimension of 20 Å have been prepared in this way (*17*). Metal films have been formed by conventional metal sputtering techniques or with the use of metallographic inks. Voltammetric data recorded at these small structures have the characteristics expected of an ultramicroelectrode (high current density, steady-state response, and immunity to ohmic drop). A procedure in which metal or carbon films are deposited on microscopic glass or quartz substrates and then the major exposed area is coated has been used to form ring electrodes (*18, 19*). Voltammograms at this geometry resemble those obtained at a disk. However, rings are advantageous because, when operated at slow time scales, the interior of the disk supports very little electrochemistry, and this region is eliminated with the ring.

Arrays of band electrodes, each operated at different potentials, offer a simple and attractive way to examine chemical changes over a few micrometers. These electrodes can be prepared by alternating layers of insulators and thin metal films as described above for the single band. Mica sheets or thin films of Mylar can be used to form insulators of micrometer dimensions (*20*). An alternate approach is to use lithograph techniques to prepare arrays of band electrodes on insulating substrates. The use of a suitably prepared mask and ultraviolet light allows spacing the bands down to ~10 μm (*21, 22*). Finer spacing can be achieved with electron beam etching techniques (*23*). Although lithographic techniques allow much more sophisticated designs of ultramicroelectrodes, they are difficult to resurface. Polishing techniques cannot be used because the structures tend to be very thin.

The instrumentation used with microelectrodes can be much simpler than that used with electrodes of conventional size. This is so because the three-electrode potentiostat normally used in voltammetric studies is unnecessary with microelectrodes—the immunity to ohmic drop found with ultramicroelectrodes is maintained with a conventional two-electrode design (*24*). Thus, only a voltage waveform generator and a suitable ammeter are required. Trace analysis with microdisks requires that currents in the picoampere range be measured. This can be accomplished with a commercial ammeter with the cell in a Faraday cage to reduce electrical interference.

Diffusion at Ultramicroelectrodes

Depending on the time scale of the experiment, voltammograms obtained at ultramicroelectrodes may differ from those obtained at electrodes of conventional size, because the dimensions of the diffusion layer can greatly exceed the dimensions of the ultramicroelectrode. The diffusion layer is the region adjacent to the electrode in which the chemical composition is altered by the electrolysis process. Mass transport through this region is one of the factors that determines the shape of the voltammogram and the magnitude of the faradaic, or electrolysis, current. Although the exact form of the current depends on the geometry of the electrode, the following generalizations can be drawn. At values of Dt/r_0^2 greater than one, where r_0 is the smallest dimension of the electrode, t is the electrolysis time, and D is the diffusion coefficient of the electrolyzed species (in centimeters squared per second), the current approaches steady state. This is so because the dimensions of the diffusion layer under these conditions greatly exceed the dimensions of the electrode, and the volume from which molecules diffuse to support the current is relatively large. The current under these conditions is proportional to the smallest dimension of the electrode. In contrast, at small values of Dt/r_0^2 the current follows the behavior expected under conditions of planar diffusion because the electrode dimensions are now larger than the diffusion layer. Voltammograms obtained under these conditions have the peak-shaped behavior seen at electrodes of conventional size, and the faradaic current is proportional to the electrode area. Example voltammograms recorded in these two different domains are given in Fig. 2. These relationships are now well understood and have been summarized in recent reviews (*25, 26*). Thus, they can be used to advantage in a number of different applications.

The solution of the pertinent equations for diffusion to spherical electrodes is relatively simple because the current is uniform across the electrode surface. In contrast, equations for the diffusion at a disk electrode are more complicated because nonuniform current density occurs at this structure. Nevertheless, the expected current can be predicted by analytical solutions as well as digital simulation procedures (*27, 28*). Similarities between the currents observed at disks and at spherical electrodes have been noted, and this provides an approximate way to obtain solutions for the more complex disk geometry (*29, 30*). Equations also exist to describe the voltammetric or amperometric current at electrodes with a geometry of a band or cylinder. Like the spherical electrode, the cylindrical electrode has a uniformly accessible area, which simplifies derivation of the equations. The nonuniform nature of the current at a band electrode complicates the solution. However, numerical and simulated results exist for the current at these structures (*31–33*). Furthermore, it has been shown that the results at band and cylindrical electrodes are very similar.

Voltammetry in Resistive Solutions

Solution resistance can severely distort electrochemical data and, until the advent of ultramicroelectrodes, precluded measurements in many solvents, because the current that flows through solution, the sum of the faradaic and residual currents, generates a potential that opposes the applied potential. The ohmic drop generated in this way will be subtracted from the applied potential difference between the working and reference electrode. At electrodes of conventional size this problem can be partially circumvented by the use of a three-electrode potentiostat. However, this procedure requires precise placement of the reference electrode adjacent to the working electrode and can result in oscillations of the electronic circuitry.

Since the currents generated at microelectrodes tend to be small, the effects of ohmic drop are considerably less than at electrodes of conventional size. Thus, one new domain that has opened with ultramicroelectrodes is voltammetry in resistive solutions. The current density in solution is greatest adjacent to the electrode surface, and thus most of the ohmic drop that does occur takes place in this region. A theoretical analysis of this problem for an ultramicroelectrode in an isotropic medium shows that the effective solution resistance is inversely proportional to the smallest dimension of the electrode (*34*). For electrodes operated under conditions where the current is steady state, the ohmic drop should be independent of the electrode size or geometry. For conditions where the electrode is operated at small values of Dt/r_0^2, both the capacitive and faradaic current are proportional to the electrode area. Thus, the ohmic drop decreases with electrode size.

These predictions have been experimentally tested. For example, at a disk electrode with a radius of 6.5×10^{-4} cm, the voltammograms are virtually undistorted by ohmic drop when ferrocene is oxidized in acetonitrile containing a concentration of supporting electrolyte one-tenth that of the depolarizer [Fig. 3; (*11*)]. Furthermore, the distortion of the voltammetric waves is relatively small even with no deliberately added electrolyte (*35*). Trace impurities in the solution may serve as the conductive species in this case.

The currents with microdisks are in the nanoampere range. With a disk electrode of conventional size ($r_0 = 0.4$ mm), at which the current shows the behavior expected for planar diffusion and is in the microampere range, voltammograms obtained with low electrolyte concentrations are distorted by ohmic drop to such an extent that they are unrecognizable even with the use of a Luggin probe and a three-electrode potentiostat (Fig. 3C). However, it is not the amplitude of the current that causes the ohmic distortion but rather its distribution through solution in the vicinity of the electrode surface. For example, with microband electrodes, which produce quasi–steady-state currents of microampere amplitude, nondistorted voltammograms are obtained for the oxidation of ferrocene under identical conditions even though large currents flow (*21, 22*).

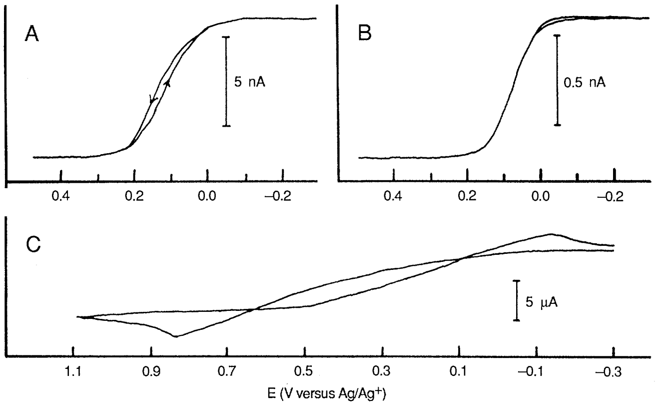


Fig. 3. Cyclic voltammograms for the oxidation of ferrocene in acetonitrile with various supporting electrolyte concentrations. (**A**) Ferrocene (1.1 mM) with 0.01 mM tetrabutylammonium perchlorate at a gold microdisk electrode (6.5-μm radius); arrows indicate scan direction. (**B**) Same as (A) but with 0.11 mM ferrocene. (**C**) Same as (A) but at a large platinum disk electrode (0.4-mm radius).

The ability to perform electrochemistry in highly resistive solutions has inspired a number of explorations into solvents in which electrochemistry is usually not conducted. Lines and Parker were the first to show that voltammetry at ultramicroelectrodes is possible in benzene containing tetrahexylammonium perchlorate (THAP) (*36*). They examined the reduction of perylene with an electrode of 30-μm diameter. The voltammetric data were difficult to interpret because intermediate values of Dt/r_0^2 were used. With the use of smaller electrodes, Howell and Wightman (*37*) were able to show that undistorted voltammograms for the oxidation of ferrocene could be obtained in solutions containing THAP (0.5M) even in solvents with a dielectric constant as low as 5.6. In solutions of benzene or toluene, the effect of ohmic drop for the oxidation of ferrocene is apparent at ultramicroelectrodes (*37*), but the problem is less severe with disks of submicrometer dimensions (*38, 39*). The voltammetric behavior is complicated on the reverse scan by a wave for the oxidation product that has been attributed to the insolubility of the charged product that appears to deposit on the electrode surface (*38, 39*) in these solvents with low dielectric constants.

In addition to solvents with low dielectric constants, other resistive media have been examined. Among the first reports was the voltammetry of ferrocene at or near the liquid-glass transition temperature of acetonitrile (*40*). Voltammograms have been recorded at potentials beyond that at which the solvent is electrolyzed. For example, Malmsten *et al.* recorded voltammograms for the reduction of pure nitrobenzene that contained 0.1M tetrabutylammonium perchlorate (*41*). Pons' group has reported waves for the oxidation of alkanes and various gases beyond the potential limit of acetonitrile (*42, 43*). In these studies the ring geometry was utilized and supporting electrolyte was not used. As noted earlier, electrochemistry can even occur in the absence of purposely added solution (*9*) with an electrode composed of two concentric rings.

For work in solutions of low dielectric constant the selection of supporting electrolyte is critical—the salt used must be soluble and must dissociate to some degree. Tetrahexylammonium salts have frequently been used. It appears that the electrolyte aggregates to form trimers and tetramers in toluene (*44, 45*). Undistorted voltammograms for ferrocene have been achieved in CO_2 under supercritical conditions with added water and tetrahexylammonium hexafluorophosphate (*46*). Presumably a similar associative mechanism occurs in this solution.

Although problems with ohmic drop are minimized with ultramicroelectrodes, the voltammetric data for resistive media reflect a number of factors that are normally not concerns for electrochemistry in conventional solutions. One is that a reference potential needs to be established. One approach is to use a quasi-reference electrode, such as a silver wire, and then refer all potentials to a standard test couple. A relative potential scale has been published which compares half-wave potentials of several compounds in toluene and acetonitrile (*44, 45*). Another factor is that migration may play a role in the mass transport of the electroactive species. When the concentration of the electroactive species exceeds that of the inert electrolyte, then the mass transport of at least one of the partners of the redox reaction will be affected by the migration process. For example, the limiting current for the reduction of cobaltecinium, the cation, is significantly increased relative to that expected under diffusion control with a low concentration of inert electrolyte (*47*). In this

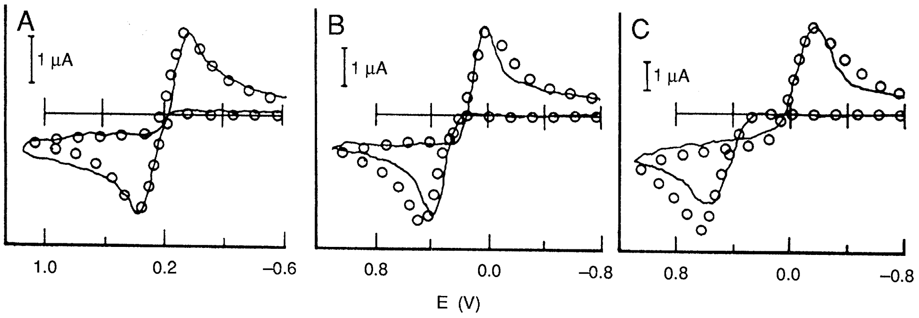


Fig. 4. Background-subtracted experimental and simulated cyclic voltammograms for the oxidation of 10 mM ferrocene in an acetonitrile solution containing 0.6M tetraethylammonium perchlorate at a gold disk electrode (5-µm radius). (—) Experimental data at scan rates of (**A**) 100, (**B**) 200, and (**C**) 500 kV sec^{-1}; (○) simulations including the effects of the cell resistance (R_u = 13 kilohms), the cell capacitance (C_d = 18 pF), and the kinetic parameters for electron transfer (k = 3.1 cm sec^{-1} and α = 0.5). [From (*7*), reprinted with permission of the American Chemical Society, copyright 1988]

case there is an increased flux of the cation to the electrode because of the generation of a neutral species by the electrolysis and, as a result, it is necessary to restore charge balance in the diffusion layer of the working electrode. In addition to the effects of migration, diffusion coefficients change with changes in supporting electrolyte concentration, because the inert salt increases the viscosity of the solution.

High-Speed Voltammetry

The capacitive nature of the impedance of any electrochemical cell precludes rapid changes in potential. Thus, electrochemical measurements with conventional electrodes have generally been restricted to the millisecond, or longer, time scale. However, the ability to make fast electrochemical measurements is desirable so that rapid heterogeneous or homogeneous reaction rates can be measured. With microelectrodes, voltammetric measurements can be made in the microsecond domain. McCreery's group was the first to demonstrate that the reduced values of resistance and capacitance found at ultramicroelectrodes lower the time constant of the cell (*48, 49*). Rather than monitor the current, they used absorption spectroelectrochemistry to measure the chemical events at the electrode surface. In this way they avoided complications associated with large charging currents. With the use of a microdisk electrode (r_0 = 3 × 10^{-3} cm) the time scale of measurement can be in the nanosecond time domain.

Electrochemistry at these very fast time scales follows planar diffusion ($Dt/r_0^2 < 1$) at ultramicroelectrodes. Therefore, the voltammetric current and the charging current are proportional to the electrode area. For this reason the ratio of the faradaic-to-background currents is exactly the same as the value that would be expected to occur at large electrodes and the current becomes uniformly distributed across the surface. Thus, background subtraction with voltammograms recorded in the absence of electroactive species is required (*50, 51*). Nevertheless, voltammograms with useful voltammetric information can be obtained at scan rates greater than 10^5 V sec^{-1} (Fig. 4) with disks of micrometer dimensions (*6–8*). Furthermore, these fast scan rates can be used in solutions of relatively high resistance (*37*).

Fast-scan cyclic voltammetry has been used to study several chemical reactions on a microsecond time scale. The fast-scan technique is particularly useful to outrun chemical reactions that consume electrogenerated products. For example, the doubly charged cation of diphenylanthracene is only stable on a microsecond time scale in acetonitrile (*37*). In another example, it has been shown that the radical cations of several aromatic hydrocarbons are stable on this time scale. Therefore, the standard reduction potentials could be determined, and these were correlated with their vertical ionization potentials (*52*). Similarly, structural changes of the reduced form of bianthrone, which occur on a microsecond time scale, have been determined (*24*). With the use of fast-scan voltammetry at ultramicroelectrodes, it has also been possible to measure heterogeneous electron-transfer reactions with rate constants exceeding 2 cm sec^{-1} (*6–8*).

Applications That Exploit the Steady-State Current

In addition to changes in the shapes of voltammograms at large values of Dt/r_0^2, other changes occur in the measured electrochemical behavior. For example, if a chemical reaction occurs between two successive electron transfers, the second step is less likely to contribute to the measured current under steady-state conditions than under conditions of linear diffusion. This is so because during the time that the electrogenerated product undergoes the chemical reaction the product of the chemical reaction may have diffused a sufficient distance such that it cannot return to the electrode (*53–55*). Similarly, catalytic reactions resulting from mediation of electrons between the electrode and an electro-inert compound in solution by an electroactive substance are less likely to be observed under steady-state conditions.

Because the current density is very high at ultramicroelectrodes, the effects of finite rates of electron transfer are much more apparent under steady-state conditions. An early kinetic study that took advantage of this feature used an ensemble of 10^6 microelectrodes (in the form of mercury droplets) with an average radius of 100 nm (*1, 2*). The rising part of the voltammetric wave has been used to determine electron transfer rates at gold-ring microelectrodes (*56*). This approach was not successful at gold-band electrodes of 5-nm width because the limiting current deviated from the predicted value (*15, 16*). It has been proposed that mass transport conditions are altered at these very small electrode dimensions, resulting in the observed change in limiting current.

Exploitation of the Small Size of Ultramicroelectrodes

Another new domain that can be explored with ultramicroelectrodes is the measurement of chemical concentrations in small volumes or at discrete, microscopic locations. By virtue of their small size, such probes could be used to make chemical measurements inside the living brain. This subject has been reviewed extensively (*57, 58*).

The small size of these electrodes has been exploited in several other applications. Baranski has described the use of anodic stripping voltammetry with ultramicro mercury electrodes for cadmium and lead in volumes as small as 5 µl [Fig. 5 (*59, 60*)]. When an ultramicroelectrode is attached to a micromanipulator, the electrode can be physically moved. In this way, heterogeneities in chemical concentrations can be examined (*61–63*). A carbon-fiber electrode encased in a small glass capillary has been used to probe heterogene-

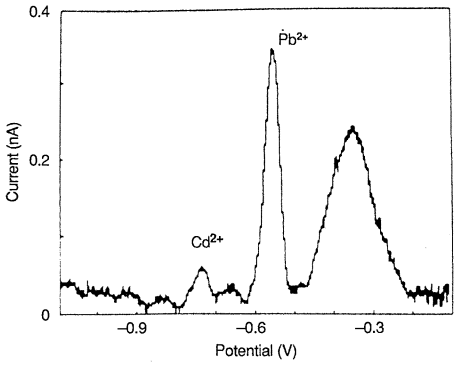


Fig. 5. Subtractive stripping voltammogram of $5 \times 10^{-8}M$ Pb^{2+} and $5 \times 10^{-9}M$ Cd^{2+} in 5 μl of nondeoxygenated $0.01M$ HCl obtained with a mercury-coated carbon-fiber ultramicroelectrode. The preconcentration sweep rate was 10 V sec^{-1}. [From (*60*), reprinted with permission of the American Chemical Society, copyright 1987]

ity at large electrode surfaces. By rastering the ultramicroelectrode through the diffusion layer of the larger electrode, a two-dimensional view of the electrochemical processes can be obtained with a resolution of 1×10^{-3} cm. Carbon-fiber electrodes have been used to measure the radial dispersion that occurs during laminar flow inside tubes (r = 0.4 mm). With the use of a voltammetric electrode that has a total diameter of 2×10^{-3} cm, the stagnant region near the wall of the tube can be clearly observed. The carbon-fiber cylindrical electrodes have been used as chromatographic detectors with very small capillary columns (*64–66*). Well-defined voltammograms can be obtained during elution of peaks from the column, and this aids in compound identification. The ultimate in "small size" applications is to combine the principles of scanning tunneling microscopy with electrochemical measurements (*67*). In this way, spatial and electrochemical measurements can be made with submicrometer resolution. Bard and his colleagues have termed this "scanning chemical microscopy."

Arrays of Microelectrodes

Closely spaced ultramicroelectrodes operated at different potentials allow the study of the reaction of unstable products electrogenerated at adjacent electrodes. For example, cation-anion annihilation reactions can occur in the space between adjacent bands operated at opposing potentials, with a concomitant generation of light (*68*). If the electrogenerated product undergoes a chemical reaction before reaching an adjacent band, lower amounts of electrochemically generated products will be observed. Since the time needed for a reagent to diffuse from one adjacent band is approximately equal to the square of the distance between the bands, very fast chemical reactions can be examined if the bands are placed sufficiently close. This has been demonstrated for the catalytic reduction of oxygen by a water-soluble hydroquinone and for the catalytic oxidation of ascorbic acid and aminopyrine by ferricyanide (*20*).

The interaction between closely spaced ultramicroelectrodes is much like the events that occur in thin-layer cells with twin, opposing electrodes. If the adjacent electrodes are coated with a conducting polymer, then the current is primarily affected by the mass transport processes in these films (*10, 69*). This provides a unique way to study these mass transport processes. With both the working and counter electrode in the film, the electrochemical cell is complete and a liquid phase is not required. It has been shown that a cell operated in this way is sensitive to the specific gas that surrounds the cell, presumably because the gases act as plasticizers and alter the film in different ways. This type of device has significant promise as an analytical sensor (*69*).

Adjacent ultramicroelectrodes coated with polymer films can be used to perform functions similar to those of solid-state electronic devices (*23, 69*). An early example was a molecular transistor. The electrical communication between two adjacent bands was controlled by adjusting the redox state and thus the conductivity of a film coated over both electrodes by a third, external electrode. Although the devices constructed to date operate on a much slower time scale than solid-state devices, their chemical basis suggests that they too will be useful as chemical sensors. The frequency response can be improved by reducing the size of the gap between adjacent electrodes.

Conclusions

It is clear that electrodes with microscopic dimensions have many unique advantages. The small size of these electrodes reduces limitations caused by the double-layer capacitance and solution resistance. Their small size also facilitates examination of chemical phenomena across very small dimensions. As these advantages become more clear and the theory of processes at these electrodes becomes more widely understood, their use in chemical applications should continue to grow.

REFERENCES AND NOTES

1. P. Bindra, A. P. Brown, M. Fleischmann, D. Pletcher, *J. Electroanal. Chem.* **58**, 31 (1975).
2. ——— *ibid.*, p. 39.
3. J.-L. Ponchon, R. Cespuglio, F. Gonon, M. Jouvet, J.-F. Pujol, *Anal. Chem.* **51**, 1483 (1979).
4. R. N. Adams, *ibid.* **48**, 1125A (1976).
5. R. M. Wightman, *ibid.* **53**, 1125A (1981).
6. C. A. Amatore, A. Jutand, F. Pfluger, *J. Electroanal. Chem.* **218**, 361 (1987).
7. D. O. Wipf, E. W. Kristensen, M. R. Deakin, R. M. Wightman, *Anal. Chem.* **60**, 306 (1988).
8. M. I. Montenegro and D. Pletcher, *J. Electroanal. Chem.* **200**, 371 (1986).
9. J. Ghoroghchian *et al.*, *Anal. Chem.* **58**, 2278 (1986).
10. M. A. Dayton, J. C. Brown, K. J. Stutts, R. M. Wightman, *ibid.* **52**, 946 (1980).
11. J. O. Howell and R. M. Wightman, *ibid.* **56**, 524 (1984).
12. K. Aoki, K. Honda, K. Tokuda, H. Matsuda, *J. Electroanal. Chem.* **182**, 267 (1985).
13. K. R. Wehmeyer and R. M. Wightman, *Anal. Chem.* **57**, 1989 (1985).
14. R. M. Penner and C. R. Martin, *ibid.* **59**, 2625 (1987).
15. P. M. Kovach, W. L. Caudill, D. G. Peters, R. M. Wightman, *J. Electroanal. Chem.* **185**, 285 (1985).
16. K. R. Wehmeyer, M. R. Deakin, R. M. Wightman, *Anal. Chem.* **57**, 1913 (1985).
17. R. B. Morris, D. J. Franta, H. S. White, *J. Phys. Chem.* **91**, 3559 (1987).
18. D. R. MacFarlane and D. K. Y. Wong, *J. Electroanal. Chem.* **185**, 197 (1985).
19. Y.-T. Kim, D. M. Scarnulis, A. G. Ewing, *Anal. Chem.* **58**, 1782 (1986).
20. T. Varco Shea and A. J. Bard, *ibid.* **59**, 2101 (1987).
21. A. M. Bond, T. L. E. Henderson, W. Thormann, *J. Phys. Chem.* **90**, 2911 (1986).
22. F. Belal and J. L. Anderson, *Analyst* **110**, 1493 (1985).
23. M. S. Wrighton, *Science* **231**, 32 (1986).
24. A. Fitch and D. H. Evans, *J. Electroanal. Chem.* **202**, 83 (1986).
25. R. M. Wightman and D. O. Wipf, in *Electroanalytical Chemistry*, A. J. Bard, Ed. (Dekker, New York, in press), vol. 15.
26. M. Fleischmann, S. Pons, D. Rolison, P. P. Schmidt, *Ultramicroelectrodes* (Datatech Science, Morganton, NC, 1987).
27. K. Aoki and J. Osteryoung, *J. Electroanal. Chem.* **122**, 19 (1981).
28. D. Shoup and A. Szabo, *ibid.* **140**, 237 (1982).
29. K. B. Oldham, *ibid.* **122**, 1 (1981).
30. Z. Galus, J. O. Schenk, R. N. Adams, *ibid.* **135**, 1 (1982).
31. S. Coen, D. K. Cope, D. E. Tallman, *ibid.* **215**, 29 (1986).
32. C. Amatore, M. R. Deakin, R. M. Wightman, B. Fosset, *ibid.* **225**, 33 (1987).
33. A. Szabo, D. K. Cope, D. E. Tallman, P. M. Kovach, R. M. Wightman, *ibid.* **217**, 417 (1987).
34. S. Bruckenstein, *Anal. Chem.* **59**, 2098 (1987).
35. A. M. Bond, M. Fleischmann, J. Robinson, *J. Electroanal. Chem.* **172**, 11 (1984).
36. R. Lines and V. D. Parker, *Acta Chem. Scand. Ser. B* **31**, 369 (1977).
37. J. O. Howell and R. M. Wightman, *J. Phys. Chem.* **88**, 3915 (1984).
38. A. M. Bond and T. F. Mann, *Electrochim. Acta* **32**, 863 (1987).
39. M. J. Pena and M. Fleischmann, *J. Electroanal. Chem.* **220**, 31 (1987).
40. A. M. Bond, M. Fleischmann, J. Robinson, *ibid.* **180**, 257 (1984).
41. R. A. Malmsten, C. P. Smith, H. S. White, *ibid.* **215**, 223 (1986).
42. J. Cassidy, S. B. Khoo, S. Pons, M. Fleischmann, *J. Phys. Chem.* **89**, 8933 (1985).
43. T. Dibble *et al.*, *ibid.* **90**, 5275 (1986).
44. L. Geng, A. G. Ewing, J. C. Jernigan, R. W. Murray, *Anal. Chem.* **58**, 852 (1986).
45. L. Geng and R. W. Murray, *Inorg. Chem.* **25**, 3115 (1986).
46. M. E. Phillips, M. R. Deakin, M. V. Novotny, R. M. Wightman, *J. Phys. Chem.* **91**, 3934 (1987).
47. M. R. Deakin *et al.*, *J. Electroanal. Chem.* **220**, 49 (1987).

48. R. S. Robinson and R. L. McCreery, *Anal. Chem.* **53**, 997 (1981).
49. ——, *J. Electroanal. Chem.* **182**, 61 (1985).
50. J. Millar, J. A. Stamford, Z. L. Kruk, R. M. Wightman, *Eur. J. Pharmacol.* **109**, 341 (1985).
51. J. O. Howell, W. G. Kuhr, R. Ensman, R. M. Wightman, *J. Electroanal. Chem.* **209**, 77 (1986).
52. J. O. Howell *et al.*, *J. Am. Chem. Soc.* **106**, 3968 (1984).
53. M. Fleischmann, F. Lasserre, J. Robinson, *J. Electroanal. Chem.* **177**, 115 (1984).
54. M. A. Dayton, A. G. Ewing, R. M. Wightman, *Anal. Chem.* **52**, 2392 (1980).
55. J. Heinze and M. Storzbach, *Ber. Bunsenges. Phys. Chem.* **90**, 1043 (1986).
56. A. Russell *et al.*, *Anal. Chem.* **58**, 2961 (1986).
57. J. B. Justice, Ed., *Voltammetry in the Neurosciences* (Humana Press, Clifton, NJ, 1987).
58. J. A. Stamford, *J. Neurosci. Methods* **17**, 1 (1986).
59. A. S. Baranski and H. Quon, *Anal. Chem.* **58**, 407 (1986).
60. A. S. Baranski, *ibid.* **59**, 662 (1987).
61. R. C. Engstrom, M. Weber, D. J. Wunder, R. Burgess, S. Winquist, *ibid.* **58**, 844 (1986).
62. R. C. Engstrom, R. M. Wightman, T. Meaney, R. Tople, *ibid.* **59**, 2005 (1987).
63. E. W. Kristensen, R. L. Wilson, R. M. Wightman, *ibid.* **58**, 986 (1986).
64. L. A. Knecht, E. J. Guthrie, J. W. Jorgenson, *ibid.* **56**, 479 (1984).
65. J. G. White, R. L. St. Claire, J. W. Jorgenson, *ibid.* **58**, 293 (1986).
66. M. Goto and K. Shimada, *Chromatographia* **21**, 631 (1986).
67. H.-Y. Liu, F.-R. F. Fan, C. W. Lin, A. J. Bard, *J. Am. Chem. Soc.* **108**, 3838 (1986).
68. C. E. D. Chidsey, B. J. Feldman, C. Lundgren, R. W. Murray, *Anal. Chem.* **58**, 601 (1986).
69. C. E. D. Chidsey and R. W. Murray, *Science* **231**, 25 (1986).

70. Research in this laboratory concerning ultramicroelectrodes has been supported by the National Science Foundation.

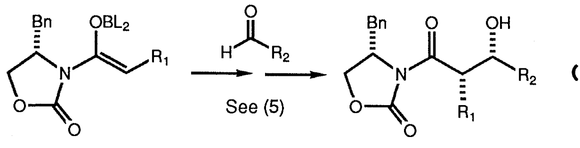
Stereoselective Organic Reactions: Catalysts for Carbonyl Addition Processes

DAVID A. EVANS

Important advances are being made in the development of stereoselective organic reactions. Some of the emerging research directions that hold forth great promise in this area deal with the development of chiral catalysts for these processes. This review attempts to unify one aspect of this field, the development of catalysts and catalyst models for the enantioselective addition of hydride and carbon nucleophiles to carbonyl substrates. Mechanistic constructs for the stereodifferentiating transition states are provided.

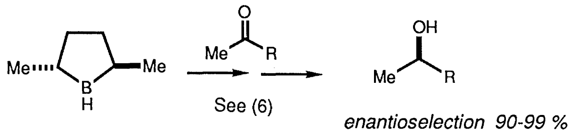
OVER THE LAST 8 YEARS THERE HAS BEEN A VIRTUAL explosion in the discovery of organic reactions that deliver levels of stereocontrol once thought to be impossible to achieve via nonenzymatic means (*1–4*). These new tools have dramatically redefined the way absolute stereochemical issues in organic synthesis are being addressed both in academic and industrial environments. A multitude of chiral reagents and an increasing number of catalysts now exist that are capable of exercising nearly perfect control over those bond constructions where new stereochemical relations are established. Several examples of reactions falling into each category are illustrated below (Eqs. 1 through 5; abbreviations: Bn, benzyl; L, ligand; R_i, some alkyl or silicon group; Me, methyl; t-Bu, *tert*-butyl; and Ac, acetyl) (*5–9*).

Stoichiometric asymmetric induction



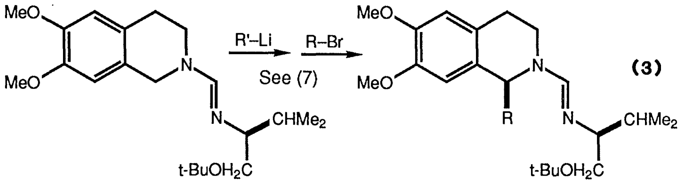
(1)

diastereoselection 96-98 %



(2)

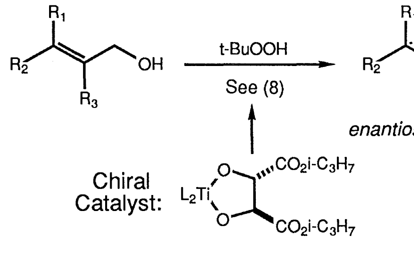
enantioselection 90-99 %



(3)

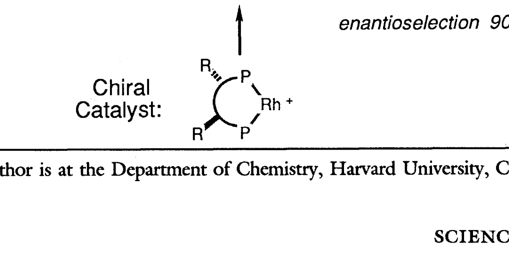
diastereoselection 93-99 %

Catalytic asymmetric induction



(4)

enantioselection 90-99 %



(5)

enantioselection 90-99 %

The author is at the Department of Chemistry, Harvard University, Cambridge, MA 02138.