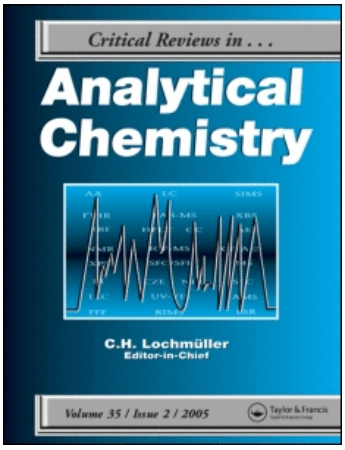

Critical Reviews in Analytical Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713400837

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Horacio A. Mottola; Harry L. Pardue

To cite this Article Mottola, Horacio A. and Pardue, Harry L.(1975) 'Catalytic and Differential Rate Methods', Critical Reviews in Analytical Chemistry, 4: 3, 229 — 280
To link to this Article: DOI: 10.1080/10408347508542674
URL: http://dx.doi.org/10.1080/10408347508542674

CATALYTIC AND DIFFERENTIAL RATE METHODS

Author: **Horacio A. Mottola**
Department of Chemistry
Oklahoma State University
Stillwater, Oklahoma

Referee: Harry L. Pardue
Department of Chemistry
Purdue University
West Lafayette, Indiana

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I. PREFACE

Although kinetics has enjoyed a recognized place in most of the other traditional subdisciplines of chemistry (inorganic, organic, and physical), it has been somewhat ignored in chemical analysis. In an analytical methodology dominated by measurements at equilibrium or in systems in which time is not a variable of importance, kinetics has been considered mainly in the context of undesirable effects, such as the sluggishness of some end-points obtained with color indicators in redox titrimetry. As a result of this, it is not surprising that textbooks in analytical chemistry have been dominated by the equilibrium view of chemical analysis, and only recently have some of them[1] turned their attention to kinetics and its application to analytical determinations. An exception to this trend is the fourth edition of what may be considered one of the most 'classical' textbooks on quantitative analysis, that of Kolthoff and Sandell. Although in the third edition[2] catalytic methods are briefly mentioned in the chapter on analysis by physical methods "for the sake of completeness", the fourth edition, which is otherwise impressive for its broad coverage and depth, includes no mention of catalytic or any other kinetic approach to determination.[3]

Even though the inclusion of kinetic considerations in analytical textbooks is in some cases (a) a mere addition to the conventionally discussed topics in analytical courses, and/or (b) a very partial coverage more misleading than authoritative (even from an educational viewpoint), these books reflect the fact that kinetics is gaining popularity among practicing analytical chemists. This increased consideration of chemical procedures based on reaction-rate measurements or exploitation of some characteristics of a chemical system not at equilibrium results from a convergence of factors, the most important of which are itemized below:

1. *The recently renewed interest, as a result of environmental and health-related concerns, in the analytical chemistry of chemical species in solutions* (particularly aqueous solutions). This singles out the first defining point in this review: *The present state of chemical development in kinetic methods of determination* is centered around the evaluation of low concentrations of materials in solution* (mostly by procedures based on catalytic effects) *and in the one-step analysis of closely related mixtures* (differential reaction rate procedures), *also in solution.*

2. The interest resulting from research, mainly in academic circles, which has in recent years been largely responsible for *the instrumentation and computer applications necessary to make kinetic analytical measurements competitive with equilibrium-based measurements.*[4-6] Both time and time-dependent signals can be measured today with high accuracy and precision, even with simple modifications or adaptations of commercially available instrumentation.[7,8] The introduction of the small laboratory computer is making it possible to foresee the time when completely automated kinetic-based procedures (sampling, handling of reagents, automated rate measurements, control of experimental parameters, and data processing) will be applied on a routine basis. The technology for this has been developed and is commercially available.

Data processing by digital computers has made possible the utilization of a large number of data points from recorded rate information, which would otherwise be of little practical value even with a large and tedious investment of valuable operator time.[9]

3. *The development of selective procedures for the determination of organic species in solution utilizing their modifying effect on catalytic reaction rates.* These developments have made available to the analyst the low limits of detection and high sensitivities of catalytic methods for the detection or determination of ordinarily noncatalytic species. The potential use of these modifying effects was recognized by Yatsimirskii in his monograph[10] and the present state of development for chemical applications has been recently reviewed.[11]

4. *The inroads that automated, flow-through, continuous determination and analysis have recently made in clinical and industrial laboratories.* Basically, in such systems, it is not necessary to bring a reaction to completion; the concentration of the sought-for component in the test solution may be continuously followed and

*Considering that *analysis* is a general term implying identification and/or measurement of *all* components, the designation *kinetic methods of determination* is preferred to the commonly used *kinetic methods of analysis.*

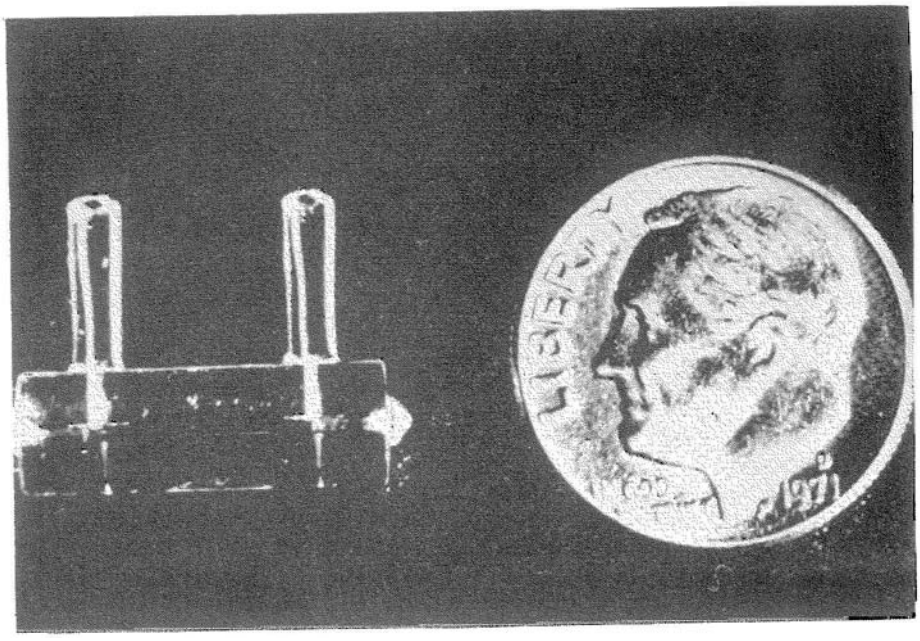


FIGURE 1. Flow cell (volume 1.2 μl) with sapphire rod end-windows (From Hamm, J. D., *Quad. Sclavo Diagn. Clin. Lab.*, 9, 149, 1973. With permission.)

compared with a known concentration of that component in a control solution. The present degree of sophistication reached by technology in flow-through measurements and its application to rapid enzymic analysis using reaction-rate techniques is illustrated by Hamm's brief account of the SMAC system (Sequential Multiple Analyzer plus Computer).[12] The instrument is composed of two modules: (a) an analytical panel for 20 channels with sampler, and (b) a computer and data-processing console. The system can perform 20 determinations/sample and handle 150 samples/hr while consuming only 325 μl of sample and a total reagent volume of 5.4 ml for the 20 determinations. High rates of analysis and the use of small sample volumes are possible, in part, because of the availability of a new flow cell having a volume of only 2 μl with sapphire end windows. These cells (one is illustrated and compared with a dime in Figure 1) can be used in the ultraviolet-visible region of the spectrum and provide a linear dependence of concentration on absorbance up to an absorbance of 2. The computer performs most of the routine operations of the sytem: correction for drift noise, warning that sample size is insufficient, standardization, linearity check, etc.

5. *The increased frequency with which research journals have published reviews on kinetic applications in analytical chemistry*. In addition to the two monographs on the subject,[10,13] over 30 reviews have appeared since 1964 when the April issue of *Analytical Chemistry* first turned attention to kinetics in analytical chemistry in its "Annual Reviews".[14]* The reviews that have appeared since 1963 are summarized in Table 1. This frequency of almost three reviews per year has resulted in some overlapping and repetition, to which this author hopes to contribute as little as possible. These repetitions would seem, however, to be justified (a) for reviews in languages other than English, and (b) by the apparent need to remind the practicing analytical chemists of the capabilities afforded by kinetic methods of determination.

Despite the foregoing developments, reaction rate (kinetic) determinations (with the exception of those using enzymes and substrates in bioclinical analysis) are still relatively lacking in practical acceptance. This is in part because of: (a) the already mentioned atavistic attitude which still looks with suspicion on measurements performed

*Tests based on catalyzed reactions, however, have been included in West's reviews on inorganic microanalysis (West, P. W., *Anal. Chem.*, 26, 121 (1954) and subsequent reviews.)

TABLE 1

Selected Reviews on Analytical Applications of Kinetics

Author, year of publication, comments	References
A. General reviews	
Mark, Papa, and Reilley, 1963. Except for a section on the application of analog computers to reaction rates, the material covered in this review can be found in Mark and Rechnitz.[13]	16
Rechnitz, 1964. First biannual review on kinetic aspects in the journal *Analytical Chemistry*. Devotes considerable attention to mechanistic studies. Review extends through Dec. 1963.	14
Yatsimirskii, Pavlova, and Skuratov, 1965. This review approximately covers the years 1962–1965 and comprehensively covers contribution from eastern Europe and Russia.	17
Rechnitz, 1966. Covers the years 1964–1966 following the pattern set by the same author.[14]	18a
Rechnitz, 1968. Covers the years 1966–1968 following the pattern set by the same author.[14]	18b
Tanaka and Funahashi, 1969. Number 8 in an excellent series of thermodynamic and kinetic concepts for analytical chemists. In Japanese. Emphasis on ligand exchange and differential reaction rate methods.	19
Guilbault, 1970. Enzyme and non-enzyme kinetic aspects combined in one review. Covers years 1968–1970.	20
Malmstadt, Delaney, and Cordos, 1972. Considerable attention given to instrumental aspects.	5a
Greinke and Mark, 1972. Covers Feb. 1970 through Dec. 1971. More method-oriented than Rechnitz's reviews.[14,18a,18b]	
Mechanistic aspects mentioned only in connection with analytical applications.	21
Mark, 1972.	22a
Mark, 1973. Gives some guidelines for developing kinetic-based analytical procedures and for reporting data and results. Discussed examples are mainly for non-catalytic determinations.	22b
Greinke and Mark, 1974. Covers Dec. 1971 through Nov. 1973. Follows pattern of earlier review by the same authors.[21]	23
B. Reviews concentrating attention on catalytic applications	
Gregorowicz and Suwinska, 1966. In Polish. Mainly inorganic redox systems.	24
Bontchev, 1970. Discussion of the mechanisms of some reactions used in catalytic determinations.	25
Gary and Schwing, 1972. In French. Mainly oxidation-reduction reactions and catalytic applications.	26
Yatsimirskii, 1973. Can be considered as a supplement to Yatsimirskii's text.[10]	27

TABLE 1 (Continued)

Selected Reviews on Analytical Applications of Kinetics

Author, year of publication, comments	References
C. Catalytic titrants and catalytic end-point indication	
Weisz and Janjic, 1967.	28
Mottola, 1969.	29
Weisz and Pantel, 1972.	30
D. Reviews with emphasis on the determination or enzymes of the use of enzymes in analytical chemistry	
Blaedel and Hicks, 1964. Includes a discussion of automatic recording of rate curves.	31
Guilbault, 1966. Covers Jan. 1960 through March 1966.	32a
Guilbault, 1967.	32c
Guilbault, 1968. Covers Jan. 1966 through Jan. 1968.	32b
Guilbault, 1970.	32d
Guilbault, 1973.	32e
Townshend, 1973. Determination of inorganic species by procedures based on their inhibition or activation of enzymes.	33
Hahn, Hoehne, and Uhlig, 1973. Review on clinical and biochemical enzymic determinations.	34
E. Reviews with emphasis on modifying effects of complexing agents on catalyzed reactions	
Bontchev, 1972. Emphasis on the use of *activators* to improve sensitivity and limit of detection in catalytic determinations.	35
Kopanica and Stará, 1973.	36
Mottola, 1974.	11
F. Reviews with emphasis on instrumental aspects of rate measurements	
Pardue, 1966.	37
Pardue, 1969. Includes a good introduction to reaction rate methods from a general analytical viewpoint.	4
Malmstadt, Delaney, and Cordos, 1973.	5b, 5c
Crouch, 1973. Application of digital and analog computing circuitry. Use of the small digital computer in analytical kinetic techniques. Detailed consideration of measurement parameters influencing signal-to-noise ratio, accuracy, and precision. Useful presentation of a unified development for mathematical expressions.	6
G. "Landolt" reactions (*The Landolt Effect** is observed as an *induction period* in reactions involving the oxidation of iodide to iodine.)	
Svehla, 1969. Good presentation of theoretical background and discussions of limit of detection, sensitivity, selectivity, and precision. No tabulation or listing of actual chemical reacting systems included.	38

*Landolt, H., *Ber. Otsch. Chem. Ges.*, 19, 1317 (1886).

TABLE 1 (Continued)

Selected Reviews on Analytical Applications of Kinetics

Author, year of publication, comments	References
H. Signal-stat methods	
Klockow, Weisz, and Rothmaier, 1973. Application to open kinetic systems.	39
I. Polarographic catalytic currents	
Sinyakova, Toropova, and Milyavskii, 1972.	40
Tur'yan, 1973. Covers catalytic systems and kinetics and mechanisms of electrode processes involved in polarography of metal complexes exhibiting ligand catalysis.	41

in dynamic systems, (b) the assumption that kinetic determinations are necessarily "too mathematically involved," and (c) the belief that kinetic determinations are confined to catalytic methods for transition-metal ions or a few anions in solution, and hence although "extremely sensitive" are limited in scope.

However, the trend detected in some analytical textbooks[1] is being observed in other areas too, and as an example of attention to the utilization of kinetics in an industrial laboratory, the present author cites a case here. A research proposal on the *"Use of Chemical Kinetic Methods in the Analysis of Inorganic and Organic Systems"*[15] was funded in 1971 under corporate research financing by Continental Oil Company for implementation in their R&D Analytical Research Section, Ponca City, Oklahoma. The project concentrated on: (a) the design and construction of versatile and flexible instrumentation applicable to different problems in spectrophotometry, potentiometry, fluorescence, etc., and (b) the incorporation of a minicomputer to process data and provide automated sample handling capabilities. Special attention was given to the construction of a stabilized light source and detector, so designed that standardization and instrument set-up do not have to be done more than once a day.

Some of the specific applications that have been made of the kinetic facilities at Ponca City since their development are listed below:[15]

1. The determination of iron by stopped-flow kinetics. This problem related to the determination of iron at low concentrations in the presence of an excess of copper ions and sulfuric acid.

2. The determination of the rate of extraction of copper ions from aqueous sulfuric acid solutions in order to evaluate several extraction additives.

3. The kinetic examination of the reaction between iron (III) and metallic copper as part of an electrochemical study. Mechanistic interpretation of the results was also provided.

4. The evaluation of a series of corrosion inhibitors accomplished by tabulation of initial rates for a given level of inhibitor. This study provided likely candidates for further evaluation. It is obvious that a test similar to this screening process can be used to select catalysts for other types of reactions.

Work in progress includes:

1. A basic kinetic study of the reaction between sulfur dioxide and iron(III), including mechanistic elucidation and the effects of catalysts and inhibitors.

2. A kinetic-based determination of bromide ion in reservoir waters. It is expected to provide a specific procedure capable of determining bromide at concentrations of about 5 ppm. The advantage of using a kinetic determination is that other ions in the reservoir water interfere with the equilibrium-based methods usually employed for bromide determination.

Besides the specific determination of given chemical species, supporting work to provide fundamental constants in order to predict reactions and side effects, and to evaluate physical and chemical behavior, are part of regular studies at Ponca City. The easy blend of a kinetically oriented analytical methodology into the service functions of an

analytical research section of a research and development laboratory also becomes obvious by examination of the applications listed above.

What the contemporary analytical chemist will be confronted with, and the future practicing analytical chemist will have to master, are *two complementary concepts:* (a) signal measurements made in systems at equilibrium, and (b) signal measurements made under dynamic conditions in systems approaching equilibrium. The choice depends on the particular case at hand, since instrumental limitations can no longer be considered an excuse to rule out the kinetic-based collection of analytical information. The academic training of future analytically oriented chemists will have to incorporate these facts in curriculum modifications.

Considering the broadness and somewhat diffuse provincial boundaries within which a kinetic-based methodology can operate, we are ready to define the scope of this review. First of all, and as advanced earlier in this preface, it is *method-oriented* for *determination of low concentrations of (usually) single species by catalytic rate methods,* and for *the simultaneous determination of closely related components of mixtures by differential reaction rate methods.* Secondly it will *attempt to characterize and organize the topics by the chemical effects involved.*

The evolved rationale of this review is illustrated with several of the most recent developments. Attention is also given to less studied but promising approaches. Instrumental aspects are well covered in other works, and in this review are considered only in connection with the aspects emphasized. Although this review is by no means exhaustive, a rather comprehensive coverage of literature from late 1972–early 1973 through about August 1974 is presented.

II. CATALYTIC RATE METHODS

A. Introduction

The term *catalytic methods* here denotes all chemical determinations directly or indirectly based on monitoring the rate of a catalyzed reaction. The criteria for catalysis as well as the name itself (catalysis: from the Greek "loosen") were originated by J. J. Berzelius around 1835–1836.[42] Berzelius' definition[42a] indicates that:

1. the catalyst is unchanged chemically at the end of the reaction.
2. a small amount of catalyst is often sufficient to bring about a considerable amount of reaction.
3. the catalyst does not affect the position of equilibrium in a reversible reaction.

These concepts lead to the *definition of a catalyst as a substance that lowers the free energy of activation of any change that can occur with a diminution of free energy.* The lowering of the free energy of activation occurs through a reaction path by which the catalyst is constantly regenerated (*the catalytic cycle*) so that, for all practical purposes, the initial concentration of catalyst remains constant. As such, *a catalyst can only increase the rate of reaction* and terms such as "negative catalysts" for substances increasing the free energy of activation should be abandoned. It must be realized that *a catalyst must influence the forward and reverse reaction rate in the same proportion.*[43] Because this is true, the last few words of the definition given in the first sentence of this paragraph are not strictly essential, but increasing the rate of a non-spontaneous process is not interesting to the analyst.

Historically, the use of a catalytic effect – that of vanadium on the oxidation of aniline by potassium chlorate – appears to have been responsible for the first kinetic-based detection[44] and determination.[45] Almost 50 years later, Sandell and Kolthoff discovered the catalytic effect of iodide on the oxidation of arsenic(III) by cerium(IV).[46] Somewhat later[47] they reported specific conditions for the catalytic determination of iodide and established the basis for catalytic determinations. Since then, the As(III)–Ce(IV) reaction has become the "preferred" *indicator reaction** for the determination of extremely low concentrations of iodide in a variety of samples, and especially for the determination of protein-bound iodine (PBI) in clinical analysis. This reaction and its catalysis by iodide have resulted in what can be termed an "institution" in itself and deserve a separate treatment in this review.

*In catalytic methods, *the main reaction in which the monitored species participates* is termed the *indicator reaction.*

TABLE 2

Types of Catalytic Effects Used in Kinetic-based Analytical Determinations

A. Homogeneous catalysis
   1. *Oxidation-reduction catalysis* – By far the most common type of catalytic effect utilized in analytical determinations. Most cases involve catalysis by transition-metal ions, but catalysis by anions is also represented.
   2. *Enzyme catalysis* – Much used in biomedical and clinical chemistry for the determination of enzymes, substrates, inhibitors, and activators. Application of enzymes to other areas of determination is receiving increasing interest.
   3. *Catalyzed ion-exchange reactions* – Includes (a) monodentate ligand exchange catalyzed by metal ions, and (b) multidentate ligand exchange catalyzed by metal ions and/or ligands.
   4. *Acid-base catalysis* – Offers poor selectivity and limits of detection. Actually many reactions catalyzed by hydronium ions are also catalyzed by some metal ions (Lewis acids). Application limited to specialized cases* or to differential simultaneous determinations if the ratio of rate constants is very large.
   5. *Exchange of oxidation states between ions of the same element* – Mechanistically resemble other oxidation-reduction reactions, but not numerous. Catalyzed by anions acting as 'bridges' for electron exchange between two oxidation states of the same species. Radioactive labeling is used to monitor the catalytic effect. (See Reference 10, p. 60 and Reference 27, p. 206.)

B. Heterogeneous catalysis
   1. *Catalytic voltammetric currents* – Mechanistically resembles homogeneous redox catalysis, involving catalytic cycles before or after the electron-transfer process at the electrode surface. Although this process is heterogeneous, analytical applications are centered on the determination of bulk concentrations in solutions.

*Some examples of particular cases of acid-base catalytic applications in analytical chemistry can be mentioned: (a) the titrations of 2,6-disubstituted phenols, keto-enol mixtures, imides, and traces of acid, with nonaqueous alkaline solutions [Vaughan, G. A. and Swithenbank, J. J., *Analyst*, 90, 594 (1965)], (b) the titration of tertiary amines and salts of organic acids in acetic acid [Vijgand, V. J. and Gaál, F. F., *Talanta*, 14, 345 (1967); Vijgand, V. J., Kiss, T. A., Gaál, F. F., and Zsigrai, I. J., *Talanta*, 15, 699 (1968); Vijgand, V. J., *Talanta*, 17, 415 (1970)].

Since these pioneer studies, the number of papers describing catalytic methods has increased year after year, to the point that nearly 100 papers (most of them by Russian chemists) have appeared in the past 2 years. Most of these papers describe direct (though a few describe indirect) methods for the determination of chemical species in solution, with a predominance of transition-metal catalysts. Methods for the determination of enzymes are not included in the 100 count.

B. Types of Catalytic Effects and Kinetic Approaches in Catalytic Rate Methods

Analytical applications in catalytically based determinations utilize a variety of catalytic effects, the most important of which are listed in Table 2. These effects are used mainly for the direct detection and/or determination of the catalytic species, although the determination of other species capable of modifying the catalyzed rate (*inhibitors* and *activators*) is receiving increased attention. Table 3 presents the translation of these catalytic effects into the analytical methodology for catalytic determinations.

The following pages contain a discussion of each of the items listed in Table 3 illustrated with recent developments in the respective areas.

1. Direct Use of Primary Catalytic Effects

a. Catalyst Determination

Primary catalytic effects are those in which the rate of a given indicator reaction is greatly increased by the presence in the system of a given chemical species: the catalyst. It is such effects that are the basis of most catalytic determinations.

The rate of any catalyzed reaction can be shown to be directly (or nearly) proportional to the initial concentration of catalyst as a result of the occurrence of catalytic cycles. This relationship is obeyed most exactly if certain reaction conditions are met, such as keeping at a constant level all variables affecting the rate (temperature, ionic strength, solvent used, solution background). The concentrations of all reactants, other than those of the catalyst and the species whose change

TABLE 3

Translation of Catalytic Effects to Analytical Methodology

A. Direct use of *primary catalytic effects*
B. Utilization of modified catalytic rates:
   1. Inhibition of catalytic rates
   2. Activation of catalytic rates:
      i. True catalysis
      ii. Promotion

in concentration is monitored, must be such as to make their effect on the rate pseudo-zeroth-order. Also, the reaction involving the monitored species is adjusted to first-order dependence. When all these requirements are met, and for the generalized reaction:

$$R + X \xrightarrow{C} \text{Products} \quad (1)$$

in which R = monitored species, X = other reactant(s) species, and C = catalyst. The following equation can be written to represent the separate and parallel contributions of the catalyzed and uncatalyzed reactions to the total rate:

$$-(\Delta[R]/\Delta t) = [R](k_u + k_c[C]_o) \quad (2)$$

in which k_u and k_c are the rate constants for the uncatalyzed and catalyzed reactions, respectively. The subscript "o" indicates initial concentration. Equation 2 is valid for rates estimated near initial reaction time, or under conditions where side reactions or the back reaction (for the indicator reaction) do not affect the rate of the catalyzed reaction. At any given time t, then

$$-(\Delta[R]/\Delta t) \propto [C]_o \quad (3)$$

or, if Δt = constant:

$$-\Delta[R] \propto [C]_o. \quad (4)$$

Equations 3 and 4 reflect the proportionality between the concentration of catalyst and rate that is used in direct determinations utilizing "primary catalytic effects." The reader must be aware that estimation of chemical concentrations is generally accomplished through measurement of a physical parameter functionally related to such concentrations. Commonly the monitoring of these physical parameters (i.e., electrode potential, absorption or emission of radiant energy, enthalpy change, etc.) results in an electrical signal detected as a current or voltage level (estimated with reference to ground). In these cases the mathematical relationship between concentration and the transfer function of the instrumental system has to be taken into account to interpret relationships between the signal change and $[C]_o$. Good discussions of these factors and their impact on the evaluation of reaction-rate data are available in the literature and the reader is referred to them for details.[6,48,49]

The general mechanism of catalyzed reactions excluding chain reactions) can be described[50] by:

$$C + R \text{ (or X)} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [CR] \quad (5)$$

$$[CR] + X \xrightarrow{k_2} \text{Products} + C. \quad (6)$$

Mathematical treatment of this mechanism as a pre-equilibrium case (for which Equation 6 being rate-determining) or a steady-state case (for which Equation 5 defines the rate-determining step) resolves the relationships to that indicated by Equation 3.

Reactions involving enzymes as catalysts are generally described with the well-known Michaelis-Menten mechanism:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} P + E \quad (7)$$

in which S = substrate, E = enzyme, and P = products. Equation 7, although with different symbolism, is equivalent to a combination of Equations 5 and 6 and it is therefore not surprising that for the determination of an enzyme (catalyst) the steady-state approximation yields an expression equivalent to Equation 2:

$$-(\Delta[S]/\Delta t) = (k_2[S][E]_o)/K_m \quad (8)$$

where K_m is the Michaelis constant = $(k_{-1} + k_2)/k_1) >> [S]$. Again the rate of change of concentration of the monitored reactant (substrate) is directly proportional to enzyme activity.*

Various methods are used to estimate the concentration of catalyst in a sample. All of them, in one manner or other, result in straight-line working (calibration) curves. Detailed discussion

*The concentration of an enzyme in solution may be expressed as *concentration of enzymic activity* and defined as activity divided by volume of solution and given in units of *katal/l*, or suitable multiples thereof. The *katal* is the unit in which enzymic activity is expressed and corresponds to the *amount of activity that converts one mole of substrate/sec.* ["Enzyme Nomenclature," Recommendations (1972) of the IUPAC and the International Union of Biochemistry, Elsevier, Amsterdam, The Netherlands, 1973, chap. 4].

determination of binary and ternary mixtures of alkaline earth ions and multicomponent mixtures of lanthanide metals. Examination of Table 5 and comparison with similar tabulations published earlier[5a,10,24,26] show a large number of methods (indicator reactions) available for the determination of some of the species. Many of these do not offer much advantage over the others and it would appear that research in this area should be pursued in the future only for systems offering unusual selectivity, sensitivity, and/or limit of detection. Determinations of osmium and ruthenium by kinetic procedures, for instance, have come to be so frequently reported that a review of 46 references has recently been published on the determination of these elements alone.[104]

The determination of enzyme activity is often

TABLE 5

Catalytic Methods for the Determination of Inorganic Species by "Primary Catalytic Effects"

(Methods published between late 1972 and approximately July, 1974.)

A. Metallic species

Species	Indicator reaction	Author(s), reference, comments
Calcium	Cu(II)–EGTA complex + 4-(2-pyridylazo)resorcinol	Funahashi et al.[51] – Metal catalysis of a ligand-exchange reaction. Calcium in the 10^{-3} to 10^{-5} *M* range is determined in the presence of magnesium. Photometric monitoring.
Cobalt	Alizarin Red S (or Tiron) + H_2O_2 in basic medium	Vzorova et al.[52] – A study of selectivity and reproducibility. Determination of 10^{-5}% of cobalt in NaH_2PO_2 and 10^{-8}% Co in high-purity HF. Analysis time 1 hr. Relative error 10–20%.
		Chuiko and Vershinin[53] – Catalytic determination of cobalt in blood without its isolation. Determination of as little as 0.2 ng in 2 ml of blood sample.
	Orange G + H_2O_2 (pH 11.4–13.5)	Costache and Popa[54] – 4–30 ng/ml. Photometric monitoring at 533 nm at 1-min intervals.
	Orange II + H_2O_2 in borate buffer.	Costache[55] – Basically the method reported in Reference 54 applied as an indirect determination of Vitamin B_{12} after sample preparation.
	Disodium 3-(4-carboxy-3-hydroxyphenylazo) chromotropate + H_2O_2	Costache[56] – Determination by evaluation of pseudo-first-order constants.
	Pyrocatechol Violet + H_2O_2 (phosphate buffer pH 11.1)	Janjic and Milovanovic[57] – Method of tangents used for the determination of 10^{-5} to 3×10^{-4} μg/ml of Co.

of them appears in several of the reviews listed in Table 1 and in the two monographs on kinetic determinations.[10,13] Table 4 presents the most frequently used methods of catalyst determination. In the determination of enzymes, initial rate measurements are common; Ingle and Crouch,[48] however, have shown that the "variable time" procedure appears superior, both from theoretical and practical considerations, when a catalyst (including an enzyme) is determined. Table 5 lists the most recently reported methods for metals and nonmetallic inorganic species utilizing "primary catalytic effects." The predominance of redox reactions catalyzed by transition metal ions and the use of organic dyes in the indicator reaction can be noted, as can the repeated use of H_2O_2 and BrO_3^- as oxidizing agents in the indicator reaction. The work of Tanaka et al.[51,97] on the determination of calcium and ammonia deserves special mention as an example of the main area of utility of catalytic effects on ligand-exchange reactions: the determination of species other than transition-metal ions. This work complements, in part, the earlier reports of Margerum et al.[9a,9b] on the

TABLE 4

Kinetic-based Methods of Determining the Catalyst Concentration

A. Derivative methods
   1. Initial rate (Catalyst concentration is derived from plots of initial rate against initial concentration of catalyst).
      a. Direct evaluation of d[Signal]/dt at $t \simeq 0$.
      b. Fixed time – Measurement of Δ[Signal] at a finite but short Δt close to $t = 0$.
      c. Variable time – Measurement of Δt necessary for a finite but short $\Delta[R]$ close to $[R]_0$.
   2. Slope. Evaluation of d [Signal]/dt (Δ [Signal]/Δt, for small increments) at any given time during the reaction.

B. Integral methods
   1. Fixed time – Integration of rate expressions over a finite, constant, but not necessarily small time interval, $t_2 - t_1$ (t_1 may be equal to zero). Under the lead to Equation 2 in the text

$$[C]_0 = \alpha(\Delta\log[R]) - \beta$$

   where $\alpha = (2.303)/k_C t_1$, $\beta = k_U/k_C$, and $\Delta\log [R] = \log [R]_1 - \log [R]_2$. Since α and β are constant, if $[R]_1$ is also held constant from run to run, plots of log $[R]_2$ against the initial concentration of catalyst will constitute a working curve. Within limited ranges of catalyst concentration, approximate straight-line plots of $[R]_2$ against $[C]_0$ can be used for catalyst estimation.
   2. Variable time – Integration of the rate expression between two finite, constant, and preestablished values of signal, such as $[R]_1$ and $[R]_2$, kept constant from run to run. Application of this treatment to the rate expression leading to Equation 2 in the text gives

$$[C]_0 = (\gamma/\Delta t) - \delta$$

   in which $\gamma = \{-\ln([R]_1/[R]_2)\}/k_C$, and $\delta = k_U/k_C$
   Working curves are obtained by plotting $1/\Delta t$ against $[C]_0$.
   3. Methods based on kinetic plots – The dependence of reaction order on the monitored species dictates the kind of plot to use. For first order dependence, plots of log [R] against time yield a family of straight lines whose slopes (designated as *pseudo-first-order-constants*) are linearly related to $[C]_0$ and can be used to construct the corresponding working curves.
   Direct measurement of the angles between the first-order plots and that for the blank or zero reaction rate gives a series of values whose tangents can be used to construct the working curve. (This method is frequently mentioned in the Russian literature as the *method of the tangents*.)

C. Methods based on the measurement of the length of an induction period
   The relationship $[C]_0 = \psi/l_i + \phi$, in which ψ and ϕ are constants, and l_i is the length of the induction period, can be found empirically in some catalyzed reactions exhibiting an induction period. In other systems the empirical relationship takes the form $[C]_0 = \theta/(l'_i)^2$, in which θ is a constant. While it resembles the "variable time" procedure, analytical applications of this approach are scarce except for the so-called "Landolt effect."

TABLE 5 (Continued)

Catalytic Methods for the Determination of Inorganic Species by "Primary Catalytic Effects"

Species	Indicator reaction	Author(s), reference, comments
Copper*	Amidol + H_2O_2	Kreingol'd and Antonov[58] – Determination of 10^{-5}–10^{-4} M Cu(II) in cesium chloride. Automatic recording of reaction profile at 536 nm.
	$TlCl_3$ + O_2 (in HCl medium)	Fel'dman and Matseevskii[59] – Fixed-time determination by quenching and evaluating the rate of thallium consumption titrimetrically.
Chromium	Meturin + H_2O_2 [catalyzed by Cr(VI)]	Kreingol'd and Panteleimova[60] – Determination of as little as 0.01–0.02 μg/5 ml.
	o-Aminophenol + H_2O_2	Kreingol'd et al.[61] – 5–10 × 10^{-6}% Cr(VI). Determination of Cr in high-purity SiO_2, KCl, Sb_2S_3, and $LiIO_3$.
	o-Dianisidine + H_2O_2	Alekseeva and Davydova[62] – 2–6 ng Cr(VI)/ml.
Gold*	Hg(I) + Ce(IV)	Eliazkova et al.[63] – 2–30 ng/ml of Au.
Iridium	Hg(I) + Mn(III) in 4.5–5.0 *M* $HClO_4$ or H_2SO_4	Yatsimirskii et al.[64] – Includes mechanistic observation assuming Mn(III) to be present as $Mn(H_2O)_6^{3+}$ or $Mn(H_2O)_5OH^{2+}$. Determination of 0.2 μg/ml.
	Fe(II) + Ag(I)	Pilipenko et al.[65] – Colloidal Ag^0 formed; stabilized with polyvinyl alcohol or gum arabic. Photometric monitoring at 530 or 540 nm.
	Mn(II) + BrO_3^-	Volynets et al.[66] – Combination of TLC and kinetic determination for microgram amounts. Estimation based on permanganate formation.
	Sb(III) + Ce(IV) or As(III) + Ce(IV)	Shcherbov et al.[67] – Monitoring of Ce(III) fluorescence.

*Copper and gold have been reported as catalysts in the decomposition of an intermediate colored complex formed in the oxidation of N-methylthiourea by iron(III) (Jankiewicz, B. and Soloniewicz, R., *Chem. Anal.* (Warsaw), 17, 1341 (1972)). Plots of the concentration of copper (or gold) against the reciprocal of the absorbance at 520 nm, which is due to the intermediate compound, are straight lines, allowing the determination of 1–10 μg of Cu(II) or 5–100 μg Au(III) in 0.1–2.5 ml.

TABLE 5 (Continued)

Catalytic Methods for the Determination of Inorganic Species by "Primary Catalytic Effects"

Species	Indicator reaction	Author(s), reference, comments
Iron	Eriochrome Black T + H_2O_2	Dumitru[68] – 0.4–2.3 μg/ml.
	Variamine Blue + H_2O_2 [catalyzed by Fe(II)]	Kreingol'd and Sosenkova[69] – 1×10^{-5}% iron in cesium chloride.
	p-Phenetidine + KIO_4	Dolmanova et al.[70] – Determination of 0.5–10 μg in boiler feed water.
Manganese	Morin–Be complex + O_2	Morgen et al.[71] – As little 0.5×10^{-3} μg/ml of Mn. Several transition-metal ions interfere.
	Malachite Green + IO_4^-	Fukasawa et al.[72] – Determination in high-purity sulfur by a combination of combustion and catalytic determination.
		Fukasawa and Yamane[73] – Determination in high-purity silicon, hydrofluoric acid, and nitric acid.
	Aromatic amines + IO_4^-	Dolmanova et al.[74] – Kinetic studies, particularly pH effects. The best limit of detection (8×10^{-5} mg/ml) was obtained with *N,N,N',N'*-tetraethyl-o-dianisidine.
	Lumogallion + H_2O_2 in basic medium	Kreingol'd and Saburova[75] – Determination in hydrofluoric acid. Analytical time: 30–40 min, 10–20% error.
Molybdenum	Sn(II) + Fe(III)–tartrate complex (pH 2.0)	Kuroda and Tarui[76] – 0.01–0.3 μg/ml of Mo(VI). Determination in sea water after ion-exchange separation.
Nickel	Diphenylcarbazone + H_2O_2 (pH 8–9)	Dolmanova et al.[77] – Determination of Ni in tantalum and niobium pentoxides by method of Dolmanova et al. (1969).
Osmium	AsO_3^{3-} + BrO_3^- coupled with methyl orange oxidation	Alekseeva et al.[78] – Recording of absorbance against time at 530 nm.
	HNO_3 + 2-naphthylamine	Khvostova et al.[79] – HNO_2 is formed and measured by equilibrium method after quenching.

TABLE 5 (Continued)

Catalytic Methods for the Determination of Inorganic Species by "Primary Catalytic Effects"

Species	Indicator reaction	Author(s), reference, comments
	Fe(II) + Ag(I)	Pilipenko et al.[80] – Monitoring of colloidal Ag^0 at 540 nm. Determination of as little as 5×10^{-4} μg in 7 ml (See Reference 65 also).
	p-Phenylenediamine + H_2O_2	Konishevskaya et al.[81] – As little as 4×10^{-5} μg/ml with 5–6% error.
Palladium	Fe(II) + Ag(I)	Pilipenko et al.[65] – See iridium above.
Rhenium	Sn(II) + Fe(III)	Kalinina and Kosyakova[82] – Fixed-time determination by measuring absorbance after 1 and 30 min of mixing. As little as 0.01 μg/ml with 5–6% error.
Ruthenium	Hg(I) + Ce(IV), or Ph_2NH + Ce(IV)	Tikhonova et al.[83] – As little as 1 μg/10 ml (15% error) determined using Hg(I). Use of Ph_2NH suggested when *the sum* of Au, Pd, Pt, Ir, Rh, and Os does not exceed 10 times the amount of ruthenium.
	Mn(III) pyrophosphate in 3–4 *M* H_2SO_4 + benzoquinone	Mueller et al.[84] – 0.01–1.0 μg/ml with 17% error.
	Cu(II) + $H_3IO_6^-$	Rozovski et al.;[85a] Rozovski et al.[85b]
	p-Anisidine + Mn(III)	Yatsimirskii et al.[64] – Claimed specific.
	Fe(II) + Ag(I)	Pilipenko et al.[80] – See iridium above.
	o-Dianisidine + KIO_4	Kalinina and Boldyreva[86a] – 10^{-5}–10^{-6}% determined in ores by method of Kalinina et al.[86b]
Selenium	AgBr + metol-hydroquinone	Markova and Kaplan[87] – Microgram amounts visually determined from amount of Ag^0 liberated on a photographic plate.
Silver	Mn(II) + $S_2O_8^=$	Pets[88] – After 8 min the reaction is quenched by cooling for 20–30 min and MnO_4^- is estimated in 3-cm cuvettes. The "sensitivity" of 10^{-8} μg/ml indicated in *Chem. Abstr.* is too good to be true.

TABLE 5 (Continued)

Catalytic Methods for the Determination of Inorganic Species by "Primary Catalytic Effects"

Species	Indicator reaction	Author(s), reference, comments
	Sulfanilic acid + $S_2O_8^=$	Aleksiev et al.[89] – Catalytic method applied to the investigation of some pathogalvanic phenomena, and attempt to correlate them with silver content of saliva after amalgam restorations in the oral cavity.
	Mn(II) + $S_2O_8^=$ in phosphoric acid medium at about 100°C	Grosse and Miller[90] – Determination of 10^{-6}% in natural materials; 6–22% relative error.
Titanium	I^- + H_2O_2 in acidic medium	Kreingol'd and Saburova[75] – Determination in tetraethoxysilane. Analytical time 30–40 min, 20–30% error.
Uranyl ion	Bixin(a corotenoid) + hν (catalyzed by UO_2^{++})	Wood[91] – 0.01–10 ppm. Unusual indicator reaction, rather free from interferences. Approximately 15% error.
Vanadium	Bromopyrogallol Red + BrO_3^- (in acidic soln.)	Costache and Sasu[92] – 0.6–6 ng/ml
	Gallic acid + BrO_3^-	Costache[93] – (1.8–7.3) × 10^{-8} g/ml.
	Bordeaux Red + BrO_3^-	Costache and Sasu[94a] – Determination in steel samples. Liteanu et al.[94b] – Limit of detection estimated as ≅ 10^{-8} g/ml by statistical analysis of noise fluctuations and by the use of the Neyman-Pearson statistical signal-detection criterion.
	Meturin + BrO_3^- (pH = 2.0 with $HClO_4$)	Kreingol'd et al.[95] – Rate independent of ionic strength. As little as 3 × 10^{-3} μg/ml determined. Method applied to "very pure" water, aluminum sulfate, and glasses.
	Chromotropic acid + BrO_3^-	Yamane et al.[96] – Initial-rate measurements. Determination of as little as 5 ng by monitoring to about 20 min.

TABLE 5 (Continued)

Catalytic Methods for the Determination of Inorganic Species by "Primary Catalytic Effects"

Species	Indicator reaction	Author(s), reference, comments
B. Non-metallic species		
Ammonia	Hg(II)–*o*-cresolphthalein complexon complex + *trans*-1,2-diaminocyclohexane-*N*,*N*,*N*',*N*'-tetraacetic acid	Tabata et al.[97] – Catalysis of ligand-exchange process. Allows the determination of microgram amounts. Cationic and anionic interferences are eliminated by preliminary distillation at room temperature.
Bromide	Methyl orange + BrO_3^-	Babkin[98] – As little as 0.1 μg/ml determined with 10% error.
Iodide	Iron(III)–thiocyanate + NO_2^- in nitric acid	Proskuryakova[99] – As little as 0.1–0.5 μg/ml. 20 to 30 min reaction time.
	Several triphenylmethane and azo dyes + H_2O_2 (in acidic medium)	Jasinkiene and Umbraziunaite[100] – Catechol Violet (2×10^{-3} μg/ml) and Bromopyrogallol (1×10^{-2} μg/ml) offer the best limits of detection.
Nitrate	Methyl orange + hν	Dodin et al.[101] – Fifteen minutes irradiation with quartz-Hg lamp. Disappearance of methyl orange followed at 500 nm. Applied to waste water and nitrogen-fertilizer industry.
Silicon	Ammonium molybdate + I^-	Morozova and Il'enko[102] – As little as 3×10^{-3} μg/ml. Interference from P, As, and Ge. Applied to aluminum alloys.
Thiosulfate	$NaN_3 + I_2$	Utsuami and Okutani[103] – 0.01 – 0.15 ppm. Sulfur compounds interfere by catalyzing the reaction. Photometric monitoring of I_2 disappearance at 350 nm.

accomplished in systems in which the catalytic effect can be termed as "primary." The nature of enzyme catalysis, which involves a specific or very selective action on a limited number of substrates (many times on a single species), restricts the number of "indicator reactions" available for enzyme determination. This is reflected by the fact that hardly any so-called "new methods" (implying different "indicator reactions") in this field have been published in recent years. Emphasis on research in enzymic determinations has been focused on instrumentation.* The so-called *Fast Analyzer Project* implemented within the MAN (Molecular Anatomy) Program at Oak Ridge National Laboratory centered in the development of automated clinical "analyzers." It was initiated by Anderson[105] and has developed versatile and sophisticated automated instruments with impact on reaction-rate (kinetic) determinations, particularly of enzymes and substrates. Recent contributions include an examination and comparison of enzymic rates and end-point determinations of substrates by use of the "Fast Analyzer,"[106] a clinical evaluation of kinetic determinations of serum triglycerides,[107] and a substantial paper on the evaluation of parameters in studies of enzyme kinetics using a small computer interfaced to the "Fast Analyzer."[108]

Lott and Turner[109] reported an instrument capable of performing 45 determinations/hr of serum lactate dehydrogenase, serum glutamic oxalacetic transaminase, and serum glutamic pyruvic transaminase. The programmed action of the system is controlled by a timing device, and the chemistry employed is that of standard kinetic procedures. The system is modular and its basic parts are accessible in most contemporary laboratories, except for the timing device, which is the heart of the system. An analog-digital readout permitting direct reading of the rate of change of absorbance over a 1-min period and a system allowing the determination of enzyme activity within 20 sec have been described by Klitzing.[110] The application of the 5010 Eppendorf automatic enzyme analyzer to the determination of serum cholinesterase has been reported by Eberhard and Kley.[111] Hoehne et al.[112] described an instrumental set-up comprising a gradient-generating component with a peristaltic pump, a mixing block, and a reaction chamber for automatic determinations of kinetic parameters of enzyme reactions. The design and evaluation of a filter fluorometer incorporating photon counting and its application to the kinetic determination of lactate dehydrogenase in serum has been described by Pardue et al.[113]

According to Kueffer and Richterich[114] *virtually any type of interference* can be eliminated in the Greiner Electronic Selective Analyzer, the GSA II, by selection of suitable assay blanks. The instrument permits monitoring of any type of zeroth- or first-order reactions as well as equilibrium determinations. A novel approach to enzyme-activity determination involves the use of silicone rubber pads containing all of the reagents needed. The approach has recently been applied to estimation of creatine kinase activity in serum by monitoring the rate of formation of reduced nicotinamide adenine dinucleotide (NADH) fluorometrically.[115a] The same principle has been previously used for the determination of cholinesterase,[115b] alkaline phosphatase,[115c] and lactate dehydrogenase.[115d] It may be mentioned here that the first kinetic determination in solid (inert) matrices was that of Pavlova and Yatsimirskii,[116] who reported a micro-determination of molybdenum based on its catalytic effect on the oxidation of rubeanic acid by hydrogen peroxide. Measurements were accomplished by reflectance estimation of the intensity of spots on filter paper, and as little as 0.002 μg of molybdenum could be determined in 1 mg or less of sea water. The authors made the interesting observation that the relationship observed between reaction rate and concentration of reactants in solution was not valid in the spot test determination.

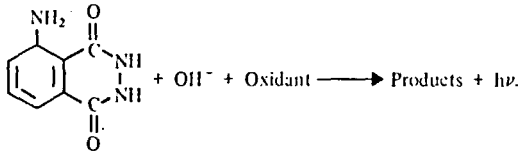
i. Primary Catalytic Determinations by Chemiluminescence

In a very limited number of indicator reactions, the catalytic effect is exerted on an ordinarily slow reaction that occurs with liberation of radiant energy (*chemiluminescence*). Chemiluminescence determinations are gaining in use and can be considered one of the areas with promise, as testified in two recent reviews on chemiluminescence in analytical chemistry.[117,118] Catalytic

*A comprehensive listing of analytical methods involving enzymes (including kinetic determinations of enzyme activity) can be found in a recent review: Fishman, M. M. and Schiff, H. F., *Anal. Chem.*, 46, 367R (1974).

effects have been reported for both organic and inorganic species,[118] although the rate effect in the case of organic species seems in many cases wrongly termed "catalytic" since the active species is consumed during reaction.

The most frequently applied indicator reaction producing chemiluminescence is the oxidation of luminol:



Luminol

5-Amino-2,3-dihydro-phthalazine-1,4-dione

The luminol reaction, first reported by Albrecht,[119] has been the basis of several methods for metal-ion determination. Table 6, taken from Seitz and Neary,[117] gives an idea of the low limits of detection afforded by this reaction. A more extensive tabulation is presented by Isaacson and Wettermark.[118] The low limits of detection make this system of interest in pollution monitoring and determinations in biological samples[120,121] as well as for metal-ion detection in liquid chromatography,[122] since the reaction is catalyzed by at least 20 metal ions.[122a] The mechanism of luminol oxidation in aqueous solution is not clear yet; the different factors determining the quantity and efficiency of light emission in chemiluminescence have, however, been studied and reported.[123] There are a few more potential "indicator reactions" besides the one using luminol, but further work is needed to assess their analytical value. The lucigenin reaction[117,118] has also received attention for the determination of chemical species in solution by chemiluminescence measurements. The limits of detection for catalysts are, however, several times lower than in the luminol system. Of interest to the analytical chemist is the concept of *liquid scintillation counting* as a measuring tool in chemiluminescence applications.[124]

ii. Primary Catalytic Determinations Based on Voltammetric Currents

Voltammetric catalytic currents have been known for a long time but their first analytical application appears to have been a contribution of the "father of polarography," Heyrovský. In an attempt to eliminate the interference of cobalt, iron, nickel, and zinc in the polarographic determination of rhenium, he treated solutions of manganous salts with hydrogen sulfide and to his surprise observed an "abnormal" increase and shift in the rhenium wave.[125] He proposed the utilization of this effect for the determination of as little as 0.02 μg of rhenium in manganous salts and indicated that the catalytic effect was "probably due" to the deposition of hydrogen catalyzed by a sulfur compound of rhenium.

A monograph is available in which catalytic and kinetic waves in polarography are considered in general,[126] and Mark and Rechnitz in their monograph[13] gave a classification (based on different proposed mechanisms) as well as examples of analytical applications. Table 7 lists some of the most recently reported studies based on voltammetric catalytic waves. Working curves

TABLE 6

Analytical Characteristics of Some Metal Ions that Catalyze Luminol Chemiluminescence*

Catalysts	Approximate detection limit, *M*	Linear range, *M*	Remarks
Co(II)	10^{-11}	10^{-11}–10^{-7}	–
Cu(II)	10^{-9}	–	Nonlinear
Ni(II)	10^{-8}	10^{-8}–10^{-5}	–
Cr(III)	10^{-9}	10^{-9}–10^{-6}	–
Fe(II)	10^{-10}	10^{-10}–5×10^{-7}	Catalyst with oxygen
Mn(II)	10^{-8}	–	Requires an amine as catalyst

*The data for Fe(II) were obtained by use of oxygen to stir the solution. All the other catalysts were effective only with H_2O_2. The conditions were 10^{-2} *M* H_2O_2, 10^{-3} *M* luminol, 0.1 *M* KOH-H_3BO_3 buffer, and cell pH between 10 and 11.

From Seitz, W. R. and Neary, M. P., *Anal. Chem.*, 46(2), 188A (1974). Copyright by the American Chemical Society. With permission.

TABLE 7

Some Recently Reported Determinations Based on "Primary Catalytic Effects" in Voltammetric Waves

Species determined	Electrode	Author(s), reference, comments
Antimony(III)	Rotating platinum disc	Taylor et al.[127] – Determination at the 10^{-4} *M* level. Method based on the increase of the limiting anodic current for Br^- in acidic media. Sample injected into a stream of electrolyte passing through a platinum coulometric detector. Application to alloys.
Molybdenum(VI)	Rotating graphite disc	Toropova et al.[128] – Determination of nanogram amounts at pH 2–3 in the presence of 0.1 *M* BrO_3 Catalytic wave at −0.1 to −0.7 V vs. S.C.E.
	DME*	Chikryzova and Kiriyak[129] – Catalytic current in solutions containing ClO_3^- and glucaric acid.
Niobium(V)	DME	Stepanova and Sinyakova[130] – Determination at the 10^{-6} *M* level by the catalytic wave of ClO_3^- in 0.5–1.0 *M* citric acid. The catalytic wave appears at a Nb:ClO_3^- ratio of 1:100.
Nitrate	Rotating silver or gold with a constantly regenerated Hg surface	Skobets et al.[132] – As little as 10 mg/l determined in solutions containing KCl, HCl and uranyl acetate. Catalytic wave regarded as due to nitric acid. Application to soil.
Titanium(IV)	DME	Sabitova et al.[131] – Determination of at least 10^{-5} *M* in acidic solutions containing $KClO_3$ or $KBrO_3$ and EDTA. $E_{1/2}$ = −0.93 V vs. S.C.E.

*DME stands for the Dropping Mercury Electrode and defines polarographic waves.

for catalyst determination are constructed by plotting the catalytic current against catalyst concentration and obtaining linear plots within certain ranges of concentration. Except in a few cases, the limits of detection cannot compare with those reported for redox catalysis in homogeneous solutions but mechanistically the process resembles redox catalysis in homogeneous solution, as exemplified by the following set of reactions proposed by Johnson et al.[127] for the catalytic enhancement by antimony(III) of the anodic wave for bromide in acidic media:

Platinum electrode: $2Br^- \longrightarrow Br_2 + 2e^-$

Diffusion layer: $Sb(III) + Br_2 \rightleftharpoons 2Br^- + Sb(V)$

This set of reactions and the use of a rotating platinum electrode not requiring electrodeposition of elemental antimony allow the continuous determination of antimony(III) in effluent streams.[127]

iii. The Sandell-Kolthoff Reaction

Very extensive work has been centered on the indicator reaction Ce(IV) + As(III) → Ce(III) + As(V) since Sandell and Kolthoff first reported the catalytic effect of iodide.[46] This indicator reaction has become the *standard* for the determination of iodide (and iodine or iodate) at very low concentrations in a large variety of samples such as table salt, water (sea, potable, and natural), grass and vegetables, filter paper, and biological materials such as serum and urine. It is useful in particular for the determination of protein-bound iodine, PBI. Actually, classified as a "colorimetric" method for iodide, the ASTM method for determination of iodide in water and waste water[133] is based on the catalytic effect of iodide on the Ce(IV)-As(III) reaction. This standard procedure calls for the quenching of the reaction after 10 min of mixing by addition of Ag^+. It is essentially a *fixed-time* determination that measures the

absorbance at about 450 nm (monitoring of Ce(IV) concentration), although it is noteworthy that for the determination of catalysts the *variable-time* procedure is superior to the fixed-time approach.[48] The catalytic action of iodide has also been used, in almost all of the conceivable ways, for the indirect determination of a large number of chemical species. Sandell and Kolthoff, in their empirical detailed study of some of the factors affecting the rate of the catalyzed reaction, noted the inhibitory effects of fluoride [which complexes cerium(IV)], mercury(II) and silver [which complexes and precipitates I^-] and cyanide.[47] Since then a variety of methods have been developed for the indirect determination of silver and mercury based on these inhibitory effects. The analytical exploitation of this indicator reaction does not stop here, though; addition of samples containing sulfur-containing ligands (which form strong complexes with mercury and silver) to an indicator reaction mixture containing HgI or AgI "regenerates" the catalyst proportionally, and allows the determination of such ligands (mercaptoacetic acid, 2-aminoethanethiol, thioacetamide, dithiooxamide, or 2,3-dimercaptoprotpan-1-ol [BAL]) at the 10^{-5} to 10^{-6} *M* level.[134]

Several kinetic observations have resulted in postulated mechanisms but excepting for the work reported by Rodriguez and Pardue,[135a] they are limited to rather specific procedures. Rodriguez and Pardue's study in 0.5 *M* sulfuric acid led them to postulates a reaction pathway that yields a rate expression satisfactorily accounting for experimental observations over a wide range of conditions. If only initial rates are considered, and since the slight dependence on As(V) concentration can be neglected [no rate dependence was observed for Ce(III)], the "simplified" rate expression becomes

$$\text{Rate} = \frac{5.82 \times 10^3[\text{Ce(IV)}][\text{As(III)}](8.46[\text{Ce(IV)}] + 3.60 \times 10^5[\text{As(III)}] + 8.46)}{1.75 \times 10^3[\text{As(III)}]^2 + (1 + [\text{Ce(IV)}])(21.5[\text{As(III)}] + 5.11[\text{Ce(IV)}])}[\text{I}]_{\text{Tot}}$$

which is indicative of the complex dependence of the rate on the reactants in the "indicator reaction." The analytical significance of such a detailed and systematic study for method development* is illustrated in a subsequent paper by Rodriguez and Pardue in which the determinations of iodide, iodate, silver(I), osmium, and mercury(II) are described at levels down to 10^{-8} *M* (3×10^{-10} *M* for osmium).[135b]

Of analytical concern, particularly in the determination of iodide in water samples, is the effect of chloride, which, ever since the report of Sandell and Kolthoff,[47] has been the subject of apparently contradictory observations.[135a,136] Keller et al.[136] have recently reviewed and reconsidered these effects and conclude that "... one can choose analytical conditions that exclude varying sample chloride concentrations as a possible source of error..." One commonly used analytical trick is the addition of a "swamping" amount of chloride to the arsenic(III) solution to maintain an essentially constant concentration of chloride, larger than that expected from reagent contamination or naturally occurring chloride in the sample.

A summary of recently published work on the application(s) of the Sandell-Kolthoff reaction is presented in Table 8. Mercury inhibition of the Ce(IV)-As(III) reaction in the absence of added iodide has been reported by Ke and Thibert.[150] These authors developed a method for the determination of mercury (in amounts ranging from 0.04 to 0.20 μg) based on this intriguing effect, for which no explanation is advanced. The same authors reported earlier[148] the determination of mercury in nanogram amounts using the same method but in the presence of added iodide.

b. Determination of Reactant(s) [Substrates]

From an analytical viewpoint, the kinetic determination of reactants (other than catalysts) has seldom been applied except in the case of substrates in enzyme-catalyzed reaction. This is mainly because of the high selectivity (and in some cases the specificity) of enzymes as catalysts. Since for substrate determinations $[S] \ll K_m$, and $[E]_0 =$

*The development of a method is usually based on empirical choices from somewhat limited experimental studies. References 135a and 135b are good examples of the analytical insight gained from detailed kinetic studies. Although they are noncatalytic in nature, the studies on cholesterol determination by the Liebermann-Burchard reaction [see Manasterski, A. and Zak, B., *Microchem. J.*, 19, 8 (1974) and Hewitt, T. E. and Pardue, H. L., *Clin. Chem.*, 19, 1128 (1973)] are worth noting in this respect.

TABLE 8

Some Recently Reported Work Based on the "Sandell-Kolthoff" Reaction

A. Determination of iodide (iodine)

Authors(s), reference, comments

Peyrin and Barbier[137] – Critical examination of the iodine determination (via iodide) in serum proteins, blood plasma, thyroid hydrolyzates, and iodide in urine.

Chung et al.[138] – A discussion on calibration curves (plots of log absorbance, absorbance, and % transmittance against iodide concentration).

Keller et al.[136] – A detailed study aimed at developing optimal conditions for the automated determination (AutoAnalyzer) of iodide in low concentrations.

Matthes et al.[139] – Determination of iodine (via iodide) after alkaline treatment in grass, clover, and filter paper using a modified procedure. Study of precision and losses in the mineralization step.

Grigoryan et al.[140] – Determination of PBI (via iodide) after alkaline fusion.

García[141] – Determination of total iodine in urine after ashing with K_2CO_3, $KClO_3$, and glycine.

Ke et al.[142] – Determination of nanogram amounts of iodine in serum.

Arcq and Arcq[143] – Use of ion-exchange chromatography and catalytic determination of thyroxine iodide. The procedure compares favorably with the isotopic technique.

Garry et al.[144] – Automated measurement of urinary iodine after dialysis.

Trimarchi et al.[145] – Discusses advantages of automated PBI determinations in serum in comparison with the manual procedure.

Knapp and Leopold[146] – Determination of thyroid hormones utilizing a specially designed automatic digital system of general application to catalytic determinations. They used nitric acid instead of sulfuric because that iodide is 20 times more active as a catalyst in nitric acid.[147]

B. Determination of inhibitors

Ke and Thibert[148] – Determination of mercury at the nanogram level. Fixed-time measurements.

Grosse and Miller[149] – Determination of silver (0.2–0.8 μg) in 1 g of silicate rocks. Interfering metals removed by solvent extraction with dithizone. The reaction is quenched with a standard solution of Fe(II) (Mohr's salt) and excess Fe(II) is titrated with Ce(IV).

constant, Equation 8 applies and

$$[S] = \Pi(-\Delta[S]/\Delta t)$$

where Π = constant = $([E]_0K_m)/k_2$, so that the initial rate is directly proportional to the initial substrate concentration. Provided that K_m is not very small, in contrast to enzyme-activity determinations, the determination of substrate concentrations appears to be favorably handled by use of the *fixed-time* approach.[48] Readers interested in this aspect of catalytic methods of determination are referred to Guilbault's most recent reviews[32d,32e] for more details and literature references. Recent examples of substrate determination are listed in Table 9. A recent report by Bergmeyer and Hagen[161] deserves separate consideration. These authors devised a system for continuous determination of glucose in which the enzyme (glucose oxidase) is fixed to a water-insoluble carrier[162] and is continuously used with a defined activity for more than 10,000 determinations. A buffer solution is continuously pumped through a closed circuit and the glucose-containing sample is introduced by means of a special applicator. An oxygen-sensitive electrode is used as detector. No doubt analytical methodology will see more and more applications of immobilized enzyme systems, as well as new schemes for continuous-repetitive determinations, in the near future. The continuous determinations of a variety of inorganic species using a flow-through system, for instance, have been reported recently.[163]

2. *Utilization of Modified Catalytic Rates*

Analytical applications of modified catalytic rates center around two main actions: (a) *Inhibition* and (b) *Activation.* Both concepts have been applied to enzyme as well as nonenzyme catalysis. Inhibition and activation in systems involving catalysts other than enzymes are mainly achieved by complexation, particularly by chelating agents that complex metal ion catalysts. Interestingly enough, on the other hand, the inhibition and activation of enzymes are mainly achieved by addition of metal ions. Recent reviews have appeared covering in some detail inhibition and activation of enzyme systems,[32e] ligand activation

TABLE 9

Recent Methods of Substrate Determination in Enzyme-catalyzed Systems

Chemical species determined	Author(s), reference, comments
Ammonia	Ishihara et al.[151] – Use of glutamic dehydrogenase and the following reaction: α-ketoglutaric acid + NH_4^+ + NADH = NAD^+ + glutaric acid + H_2O Initial rate measurement by monitoring absorbance at 340 nm. Determination in blood plasma. (NADH: reduced *N*icotinamide *A*denine *D*inucleotide, NAD)
	Jacobs and Olthuis[152] – System like that in preceding entry. Determination in plasma. Advantages of a kinetic approach over equilibrium measurements cited. (Note: The determination of ammonia-nitrogen in water and sediments utilizing the enzyme-catalyzed system referred to here along with an equilibrium (end-point) determination has been reported recently: Verdou, H., *Water Res.*, 7, 1129 (1973). Reaction-rate determination appears possible and may be advantageous.)
Adenosine triphosphate	Lemasters and Hackenbrock[153] – Continuous measurements in mitochondrial suspensions using firefly luciferase luminescence (McElroy, W. D., Seliger, H. H., and White, E. H., *Photochem. Photobiol.*, 10, 153 (1969)). Quantitative estimation of ATP is possible at any time by addition of ATP standard.
Creatine	Lau and Guilbault[154] – Determination of creatine in urine. Use of creatine kinase, two coupled indicator reactions, and fluorometric monitoring of NADH oxidation at 460 nm.
Glucose	Llenado and Rechnitz[155] – Ion-electrode-based automatic determination. The reported system is usable for equilibrium as well as kinetic measurements. For technical reasons a *fixed-time* approach is favored in kinetic determinations, by oxidizing glucose: $\text{Glucose} + H_2O + O_2 \xrightarrow{\textit{Glucose oxidase}} \text{Gluconic acid} + H_2O_2$ $H_2O_2 + 2\,I^- + 2\,H^+ \xrightarrow{\textit{Mo (VI)}} I_2 + 2\,H_2O$ The decrease in the concentration of I^- is followed with an iodide-selective membrane electrode.
D-Glucose	Cheyne and Yeomans[156] – Determination in plasma and urine utilizing the LKB 8600 reaction-rate analyzer. Comparison is made with manual determinations of glucose by the same enzymic method.

TABLE 9 (Continued)

Recent Methods of Substrate Determination in Enzyme-catalyzed Systems

Chemical species determined	Author(s), reference, comments
D-β-Hydroxybutyrate	Chandrasekaran and Lord[157] – Automated determination in blood (LKB Model 8600 Reaction Rate Analyzer) utilizing 3-hydroxybutyrate dehydrogenase: D-β-hydroxybutyrate + NAD ⇌ acetoacetate + NAD + H^+ pH 8.5; rate monitored at 340 nm.
"Inorganic phosphate"	Hwang and Cha[158] – Use of purine nucleoside phosphorylase and xanthine oxidase as indicator enzymes. Fixed-time procedure quenching with EDTA (which binds Mg^{++} acting as activator for the phosphorylase). Uric acid formed in the reaction: Hypoxanthine + H_2O + O_2 $\xrightarrow{xanthine\ oxidase}$ Uric acid + 2 H_2O is monitored at 293 nm.
Uric acid	Haury and Fried[159] – Determination in serum according to the concerted action of uricase and catalase.
	Lum and Gambino[160] – Uricase method for use with the DuPont Automatic Clinical Analyzer and comparison of four methods for the determination of uric acid (copper-chelate, phosphotungstate, manual uricase, and automated kinetic uricase).

in metal complex catalysis (redox),[35] and ligand inhibition and activation.[11]

a. Inhibition

Species combining with the catalyst to form some sort of complex that either exerts diminished catalytic action (*partial inhibition*) or is completely inactive as a catalyst (*total inhibition*) may be determined because, obviously, their effect on the reaction rate will be proportional to the concentration of inhibitor. It has been general practice in the determination of inhibitors to follow the decrease in reaction rate (commonly the *initial rate*) in systems which contain a constant amount of catalyst and to which increasing amounts of the inhibitor have been added to construct working curves. This approach offers good limits of detection but limited dynamic range of concentrations amenable to determination. With some sacrifice in limit of detection but considerable extension of the concentration range for determination, the rather novel *catalytic endpoint indication,*[29] also termed *catalimetric titration,*[10] is ideally fitted for the determination of inhibitors. The approach involves two consecutive reactions: (a) the *titration reaction,* in which a *catalytic titrant* is added to the sample and reacts rapidly and stoichiometrically with the sought-after species, and (b) the *indicator reaction,* which involves the monitored species and can only occur at a noticeable rate, under the given experimental conditions, once an excess of catalyst (titrant) is present in the system. The end point of the titration is then detected from the sudden increase (or decrease) of the monitored species, and the amount of catalyst needed to reach the end point is directly proportional to the amount of inhibitor present in the sample. If the catalyst is added at a constant rate and the change of signal with time is recorded, the resulting titration curve shows a *pseudo-induction period* whose length is proportional to the amount of inhibitor present as shown

in Figure 2.[164] Simple electronic switching and timing may then be used to measure the length of this pseudo-induction period.[165] The concept of catalytic end-point indication was introduced by Yatsimirskii and Fedorova back in 1962.[166] These authors performed a "simulated" titration by following, photometrically, the reaction in acidic solutions containing equal amounts of silver ion

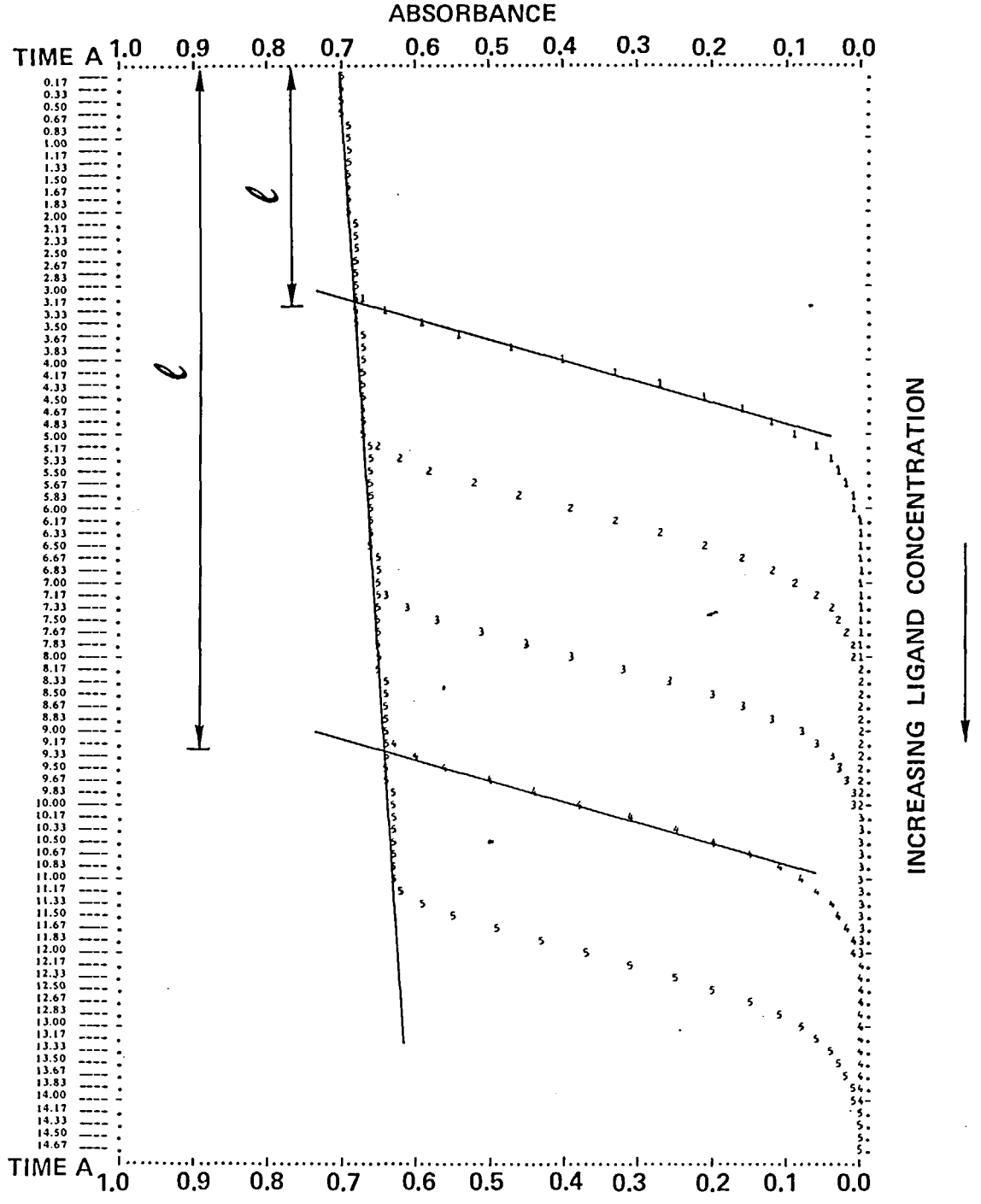


FIGURE 2. Computer-simulated curves for catalytic end-point indication assuming absorptiometric monitoring of one of the reactants in the "indicator reaction." The "normal catalytic cycle" is considered to occur by pre-equilibrium kinetics. ℓ: length of "pseudo-induction period" on which working curves for ligand determination are based.(Simpson, B. E., M. S. thesis, Oklahoma State University, Stillwater, Okla., 1973. With permission.)

and increasing amounts of titrant (iodide catalyst); the indicator reaction was the widely used Ce(IV)-As(III) system. Figure 3 is an adapted plot from Reference 166b. So long as silver was in excess, the addition of iodide resulted only in an increase in the amount of silver iodide formed; thus up to the equivalence point the "free" iodide concentration was about 9×10^{-9} *M*, below the concentration threshold required for a noticeable rate of the indicator reaction. As soon as an excess of iodide catalyst was present in the system, the slope of the first-order plots (tan α) changed drastically with increasing catalyst concentration. The convenient techniques of constant-rate addition of titrant and automatic recording of photometric titration curves[167] have been adopted and extended to potentiometric as well as colorimetric and biamperometric indication of end point.[30,168] Recent work by Hadjiioannou et al.[168-170] points to the wide range of inhibitor concentrations that can be determined as well as to the good accuracy and precision afforded by automatic (or semiautomatic) titrations with catalytic end-point indication. The following examples can be cited: (a) mercury was titrated in the 5×10^{-8} to 10^{-4} *M* range and iodide in the 10^{-8} to 10^{-4} *M* range by addition of known excess of standard mercury(II) solution with a precision and accuracy of $\simeq$ 0.7%;[169a] (b) by use of the periodate-diethylaniline indicator reaction and manganese(II) as catalytic titrant, 10^{-7} to 10^{-4} *M* EDTA was determined with accuracy and precision in the neighborhood of 0.5%;[169a] (c) copper, lead, mercury, cadmium, and zinc were also determined in the same concentration range as in the EDTA determination, and with comparable precision and accuracy, by addition of a known excess of standard EDTA solution and back-titration with manganese(II);[169a] (d) in the systems described in (b) and (c), the periodate concentration was monitored with an ion-selective electrode; accuracy and precision for EDTA and metal ions in the 10^{-5} to 10^{-3} *M* range was about 1%.[169b] Milligram amounts of copper and manganese have been titrated with EDTA using the oxidation of phenolphthalein by H_2O_2 as indicator reaction.[171a] The oxidation of aromatic amines by hydrogen peroxide has also been used as an indicator reaction in the chelatometric titration of manganese(II).[171b]

The masking and demasking of metal ions by complexing agents allow a variety of titrimetric conditions to be covered with a single indicator reaction and catalytic titrant; examples can be found in the literature.[169a,172] Some of the factors to be taken into account in complexometric titrations with indicator reactions involving electron exchange have also been discussed.[173] An up-dated review on catalytic end-point indication will be published elsewhere.[174]

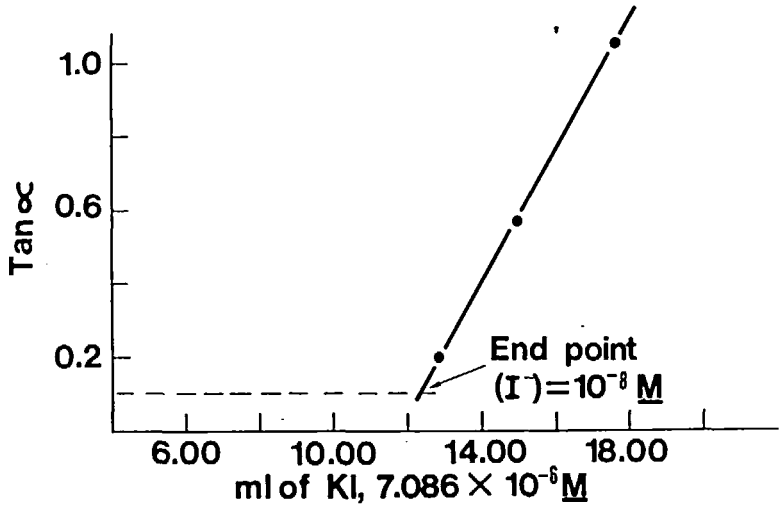


FIGURE 3. Slope of first-order plots against volume of titrant added in the titration of $4.36_4 \times 10^{-6}$ *M* silver nitrate using the Ce(IV)–As(III) reaction for catalytic end-point indication, (Yatsimirskii, K. B., and Fedorova, T. I., *Zh, Anal. Khim.*, 18, 1300, 1963.)

b. Activation

In a broad sense *activation* occurs when the addition of a given chemical species (the *activator*) increases the rate of a given chemical reaction by providing a reaction path requiring a lower activation energy. In catalytic rate considerations, however, the term is being used with a more restricted interpretation: it refers to an increase of the catalytic rate by addition of the so-called *activator.*[35] Analytical applications of activation seem to be limited to modification of catalytic rates by complexation of metal ions in electron-transfer catalysis,[11] especially that involving transition-metal ions and chelating agents. This is not surprising considering that any change in coordination results in a change in redox properties. Stabilization of intermediate oxidation states involved in catalytic cycles by complexing agents seems to result in *true metal-complex catalysis,* in which the complex acts as a catalytic species, offering a reaction path with lower activation energy than that presented by the metal-ion catalyst itself. In other instances, however, during the course of the catalytic cycle the "new" catalytic species loses identity through competitive reactions that halt the "activating" effect. These competitive reactions may result in the destruction of the ligand or its complexation by other species being formed in the system. In order to distinguish this effect from true metal-complex catalysis, the designation of *promotion*[11,175] seems adequate.* No analytical application of a recognized case of promotion on a catalyzed reaction seems to have been published as yet. The probable effect, however, will be confined to what has recently been observed in some reactions involving intermediate oxidation states of chromium:[175] a rather brief, and in some instances transient, modifying effect. Figure 4 shows the typical behavior, characterized by an initial promoting action. As soon as the rate modifier is destroyed (or inactivated), the overall rate tends toward that of the indicator reaction in its absence. With adequate mixing and signal-monitoring devices, application of the initial-rate** measurements allows the determination of the rate modifier.[175] As in true metal-complex catalysis, obviously, an excess of modifier should provide a system for the determination of catalyst with improved sensitivity and limit of detection. In any event, activation of catalyst is a relatively new mode of application of catalytically based rate methods. It offers two distinguishable advantages: (a) it allows an increase in sensitivity (and sometimes a lower limit of detection) in the determination of the catalyst itself,[35,176] and (b) it extends the application of catalytic methods to the determination of normally noncatalytic organic species at low concentrations, particularly chelating agents.[7,11] A recent publication by Bontchev and Aleksiev,[177] is significant to the use of "activators" in chemical analysis. Studying the effect of nitrogen-containing ligands on silver-ion catalysis, these authors postulated that the presence of neutral ligands in the coordination sphere of the catalyst leads to a decrease of the free energy of the coordination-sphere electronic arrangement during the change in oxidation number of the catalyst. This results in an acceleration of the limiting stage of the reaction, and hence of the overall rate. Their work, based on catalysis by Ag(I) of the sulfanilic acid-$S_2O_8^=$ indicator reaction, covered the following ligands (listed in order of decreasing action on the activation process): phenanthroline > dipyridyl > ethylenediamine > pyridine > 2-methylpyridine and 4-methylpyridine > 4-aminopyridine > ammonia. Of interest in future developments in the selection of activators in homogeneous catalytic reactions is their successful application of the Marcus theory[178] of decrease of the free energy of the limiting step in a redox reaction in solution.

An overview of recent analytical utilizations of activation of catalytic processes is given in Table 10. A sort of *pseudo-activation* may occur when an active catalyst (or promoter) is blocked from participation in a rate-enhancing process by complexation and addition of a given chemical species releases or displaces the active catalyst or promoter from its complex: Illustration of this can

*The word *promoter* was first used in the English specification of a patent by the Badische Anilin and Soda Fabrik in 1910, in connection with the Haber process (see Reference 42a). In industrial heterogeneous catalysis it is defined as *a substance which added to a catalyst disproportionately benefits its activity or selectivity* (Catalog No. 500, The Harshaw Chemical Co., Cleveland, Ohio, p. 27). The concept of promotion adopted in this review follows suggestions of Martell regarding catalytic effects of metal chelate compounds [Martell, A. E., *Pure Appl. Chem.*, 17, 129 (1968)].

**In some cases it should be possible to apply the variable-time procedures successfully.

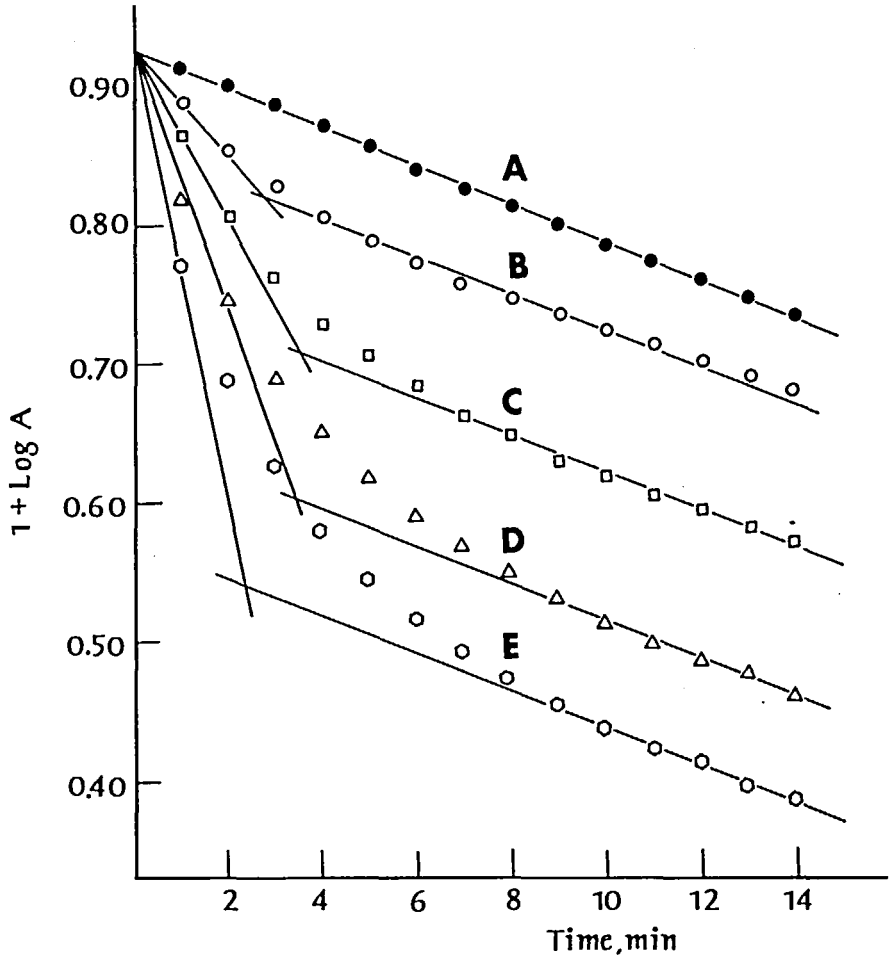


FIGURE 4. First-order plots for the reaction of tris(1,10-phenanthroline) iron(II) with chrominum (VI), showing oxalic acid promotion. Cr(VI): 8.33×10^{-5} *M*, ferroin: 7.60×10^{-5} *M*, sulfuric acid: 0.25 *M*. Concentration of oxalic acid added. A. 0. B. 1.00×10^{-5} *M*. C. 2.00×10^{-5} *M*. D. 3.00×10^{-5} *M*. E. 4.00×10^{-5} *M*. (From Eswara Dutt, V. V. and Mottola, H. A., *Anal. Chem.*, 46, 1092, 1974. Copyright by the American Chemical Society. With permission.)

be found in some applications of catalytic end-point indication.[169a,172]

C. Sensitivity and Limit of Detection in Catalytic Rate Methods

It is well recognized that the major advantages of catalytic determinations are their low limits of detection and high sensitivities. When low concentrations of materials are involved the following three terms are generally recognized:[190,191] (a) sensitivity, (b) detection limit, and (c) limit of guarantee of purity.

Sensitivity is one of the most misunderstood terms in chemical analysis and allied disciplines. Although clearly different from "limit of detection," it is often used synonymously with that phrase in many authoritative textbooks and journal articles. The distinction between these two terms in quantitative spectrometric methods has recently been described.[192] The concept of sensitivity is being accepted as representing the value of the slope of the calibration (working) curve. Catalytic rate methods yield information which can be translated into linear working curves, and sensitivity can be evaluated by comparisons of these working curves with each other within a concentration boundary condition.[167b]

The *detectability* or limit of detection signifies the "smallest quantity of material that can be detected with certainty,"[193] and as such is intimately related to the standard deviation of the blank values. Statistical evaluation of the blank

TABLE 10

Recent Analytical Applications of Activation of Catalytic Rates

A. Inorganic species

Chemical species determined	Activator(s)	Author(s), reference, comments
Copper	2,2′-Bipyridine	Dolmanova et al.[179] – Catalytic oxidation of hydroquinone with H_2O_2. Determination of 10^{-8}% in sea water and in hydrochloric acid.
Cobalt	*o*-Phenylphenol	Dolmanova et al.[180] – Indicator reaction: diphenylcarbazone + H_2O_2 at pH 9.2–9.5. Determination of as little as 1×10^{-5} μg/ml.
Chromium	γ-Picoline	Dolmanova et al.[181] – Determination of as little as 1.8×10^{-6}% in GaAs after previous separation by partition and ion-exchange chromatography. Interfering species accompanying chromium separated by extracting with dithizone into carbon tetrachloride. Indicator reaction: *o*-dianisidine + H_2O_2.
	Carboxylic acids (*p*-aminobenzoic, oxalic, citric, salicylic, and sulfosalicylic; also nitrogen-containing ligands: pyridine, γ-picoline, quinoline, 2,2′-bipyridine, and 1,10-phenanthroline)	Dolmanova et al.[182] – Indicator reaction: *o*-dianisidine + H_2O_2.
Iron	2,2′-Bipyridine	Rychkova and Rychkov[183] – Indicator reaction: *o*-toluidine + periodate (pH 4–6). As little as 0.5 μg determined.
Manganese(II)	1,10-Phenanthroline	Tiginyanu and Oprya[184] – Indicator reaction: iodide + periodate at pH 5.2–5.5, with starch. Determination at the 10^{-8} *M* level with 10–12% error.
	Ethylenediamine	Bartkus and Jasinskiene[185a] – Indicator reaction: 5-(2-hydroxy-3-sulfo-5-chlorophenylazo)barbituric acid + H_2O_2 at pH 7–11. Determination of as little as 0.3 μg/50 ml.
	2,2′-Bipyridine, 1,10–phenanthroline, and ethylenediamine	Bartkus and Jasinskiene[185b] – Indicator reactions: Pyrocatechol Violet (Bromopyrogallol Red, or Pyrogallol Red, or Lumomagneson, or Stilbazo, or sodium carminate, or Alizarin Red C) + H_2O_2. A significant activating effect is observed only at pH 9.2. Mn(II) is apparently detectable at the 10^{-11}-*M* level. Possible mechanisms for the activating effects are discussed.

TABLE 10 (Continued)

Recent Analytical Applications of Activation of Catalytic Rates

Chemical species determined	Activator(s)	Author(s), reference, comments
Molybdenum	Hydroxy acids (malic, tartaric, and trihydroxyglutaric)	Chikryazova and Kiriyak[186] – The polarographic catalytic current in solutions containing Mo(VI) and chlorate ions is increased by hydroxy acids. The increase is ascribed to formation of a surface-active intermediate involving Mo(VI), the dianion of the acid, and chlorate ion.
Nickel	*o*-Phenylphenol	Dolmanova et al.[180] – Indicator reaction: diphenylcarbazone + H_2O_2 at pH 9.2–9.5. Determination of as little as 10^{-3} μg/ml.
Rhodium	Thiosemicarbazide	Ezerskaya and Kiseleva[187] – Catalytic polarographic (hydrogen) currents in acetate buffer (pH 4.6). Two catalytically active complexes were identified, containing different proportions of activator. Determination of as little as 4×10^{-7} *M*.
Vanadium	8-Hydroxyquinoline	Pantaler and Chernomord[188] – Indicator reaction: 1,5-diphenyl-3-aminopyrazoline + BrO_3^-, catalyzed by vanadium(V). Threshold sensitivity reported as 5×10^{-7}%.
3. Organic species		
Phthalic acid	Carboxylic acids	Strizhov and Tur'yan[189] – The catalytic pre-wave of indium(III) is increased by the presence of carboxylic acids in the order: benzoic < *o*-acetylsalicylic < salicylic < phthalic < isophthalic < pyromellitic < trimellitic. Phthalic acid was determined in the concentration range 2.5×10^{-6} to 5×10^{-4} *M*.

fluctuations permits an evaluation of the limit of detection.[191,193] In catalytically based methods this blank is represented by the rate of the uncatalyzed reaction or, in case of modified rates, by the rate of the unmodified catalyzed reaction.

The *limit of guarantee of purity*[194] is aimed at answering the question of what minimum purity can be guaranteed if a substance that might be present cannot be detected because the experimental value is below the limit of detection. Its evaluation is also based on the mean of the blank values and the corresponding standard deviation.[193]

Yatsimirskii's monograph,[10] the first review of kinetic methods of analysis, briefly considers the minimum concentration of a substance accessible to measurement by a catalytically based procedure. The treatment used is more closely related to limit of detection than to sensitivity. In spite of the confusing terminology, the review is well taken as showing the potentiality of catalytic methods in comparison with equilibrium determinations. Yatsimirskii's treatment is limited to a particular case of initial-rate measurement. To illustrate the point in a broader manner, the simplified model reaction illustrated by Equation 1 will be analyzed in three ways: (a) initial rate (derivative), (b) variable time (integral), and (c) fixed time (integral). The model reaction is used to develop mathematical relationships among the different experimental factors affecting detectability and sensitivity. If initial-rate measurements are performed, Equation 2 can be rewritten as

$$[C]_o = \left(-\frac{d[R]}{dt} \cdot \frac{1}{k_c[R]}\right) - \frac{k_u}{k_c} \qquad (9)$$

with $-d[R]/dt$ = initial rate, IR (when $[R]$ is very close to $[R]_o$). Hence, plots of initial rate against

TABLE 11

Linear Relationships Between Sought-for Species and Kinetic Quantities in Common Cases of Catalytically Based Determinations*

Method	Detectability	Sensitivity
Initial Rate (*derivative*)	$[C]_0 = -(\frac{d[R]}{dt}) \cdot \frac{1}{k_c[R]_0} - \frac{k_u}{k_c}$	$\frac{\Delta(d[R]/dt)}{\Delta[C]_0} = k_c[R]_0$
Variable Time (*integral*)†	$[C]_0 = \frac{K}{\Delta t k_c} - \frac{k_u}{k_c}$	$\frac{\Delta(1/\Delta t)}{\Delta[C]_0} = \frac{k_c}{K}$
Fixed Time (*integral*)†	$[C]_0 = -\frac{ln[R]_1}{k_c t_1} + \frac{ln[R]_0}{k_c t_1} - \frac{k_u}{k_c}$	$\frac{\Delta(ln[R]_1)}{\Delta[C]_0} = k_c t_1$

*Expressions restricted to catalyst determination and to conditions in which Equation 2 in text is valid.

† The classification of integral refers to the mathematical treatment of Equation 2; the same expressions are valid in case of initial-rate estimation by the fixed- or variable-time procedure.

the concentration of catalyst will be represented by Equation 2 with $[R] = [R]_0$. The intercept, $k_u[R]_0$, will be associated with limit of detection, and the slope, $k_c[R]_0$, will be associated with the sensitivity. The minimum value of $[C]_0$ appears when the initial rate to be measured can be minimized and k_c and $[R]_0$ can be made large.

As already mentioned, $k_c[R]_0$ will define the sensitivity. This can be confirmed by defining sensitivity as $\{\Delta(IR)/\Delta[C]_0\}$ = slope of working curve, for at two different concentrations of catalyst

$$\Delta[C]_0 = [C]_{02} - [C]_{01} = \{(IR_1)_1 - (IR)_2\}\frac{1}{k_c[R]_0} \quad (10)$$

Hence $\frac{\Delta(IR)}{\Delta[C]_0} = k_c[R]_0$, and as stated the larger $k_c[R]_0$ the greater the sensitivity. Similar reasoning can be applied to the variable-time and the fixed-time approaches to obtain expressions similar to Equations 9 and 10. Table 11 displays these expressions and, within the assumptions and restrictions imposed on the reaction of Equation 1: (a) the value of $[R]_0$ appears to be critical only in the case of the initial-rate (derivative) approach; (b) in the variable-time procedure two factors have opposing effects on the detectability and sensitivity; those factors are the minimum difference in signal amenable to measurement and the maximum time interval; and (c) in the fixed-time procedure, the critical variable is the time elapsed before measurement. In all cases, however, k_c must be as large as possible and k_u as small as possible, since the ratio k_u/k_c is critical considering limit of detections. It becomes apparent that reporting a value of the sensitivity (or limit of detection) for a catalytic (or for any other reaction-rate method) without qualifying remarks on the manner in which these values have been obtained may be very misleading.

As already stated, the literature does not clearly distinguish between detectability and sensitivity, although what commonly is referred to as "sensitivity" or "threshold sensitivity" has to be taken as a close approximation of the detectability. Catalytically based determinations of single components (one measured quantity) yield linear relationships,* and an evaluation of sensitivity should involve the determination and comparison of the slopes of working (calibration) curves. In the determination of very small amounts of materials and for the evaluation of the quantities discussed here, linear calibration and linear analytical functions are necessary. If required, all functions must be made linear by suitable transformation of variables.

Considering the importance of detectability and sensitivity in catalytic rate methods, the author of this review feels it necessary that future work should critically examine these variables. Recognition of the basic difference

*The exploitation of kinetic differences for the determination of more than one catalytic species without prior separation has, however, been demonstrated by Rodriguez and Pardue[135b] and by Worthington, J. B. and Pardue, H. L., *Anal. Chem.*, 42, 1157 (1970).

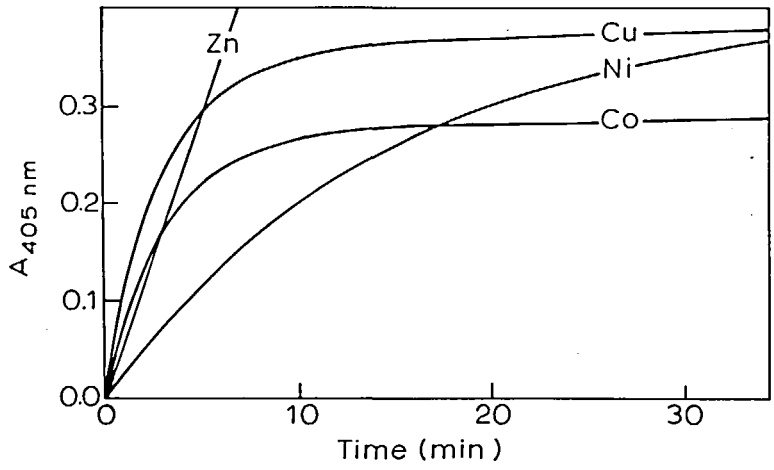


FIGURE 5. Hydrolysis of leucine-*p*-nitroanilide by Zn-, Cu-, Ni-, and Co-aminopeptidase in the presence of EDTA. The peptidases were prepared by reactivating the apoenzyme with a two fold excess of the various metals. The reaction was started by adding the enzyme to the EDTA-containing substrate. The final enzyme concentration was 0.75 μM. (From Lehky, P. and Stein, E. A., *Anal. Chim. Acta*, 70, 89, 1974. With permission.)

between limit of detection and sensitivity should result in an unified manner of reporting these parameters which would permit critical comparisons of methods.* In a recent article temporarily unavailable to the author of this review, Liteanu et al.[195] have estimated the photometric detection limit of the kinetic method for determining vanadium by its catalytic action on the bromate-Bordeaux R indicator reaction; by use of the Neyman-Pearson statistical signal detection criterion and statistical analysis of the noise fluctuations, a value of 1×10^{-8} g/ml was obtained. Also recently, Proskuryakova et al.[196] reviewed some mathematical expressions used in the calculation of the minimum amount, n_{min}, of a given chemical species that can be determined by a method based on absorbance measurements, and recommended the expression: $n_{min} = (A - A_0)/b = 0.05/b$ (in which A and A_0 are the absorbances of the sample and the blank, respectively, and b is the slope of the calibration curve) for photometric and for kinetic determinations by the fixed-time procedure.

One of the most interesting chemical contributions on extending the limit of detection in catalytically based determinations is a recent paper by Lehky and Stein.[197] These authors report an enzymic method which, under ideal conditions, would allow the determination of zinc concentrations below 1 pg/ml. Besides the low limit of detection, the selectivity is also attractive, since 0.1 ng/ml of Zn can be determined with reasonable accuracy even in the presence of 10- to 100-fold excesses of most other metals. These characteristics are made possible by use of a metal-free inactive apoenzyme. The possibility of removing the metal (by means of a complexing agent) from a metalloenzyme to obtain the corresponding apoenzyme, whose activation would provide a very selective procedure for the determination of the prosthetic metal, was first pointed out by Townshend and Vaughan.[198] The reagent for zinc used by Lehky and Stein[197] was obtained by removing zinc from pig kidney aminopeptidase, a commercially available metalloenzyme, by use of EDTA. The aminopeptidase activity was determined photometrically by measuring the rate of release of *p*-nitroaniline from l-leucine *p*-nitroanilide. Copper(II), cobalt(II), and nickel(II) also reactivate apoaminopeptidase (Figure 5), but limits of detection for these species are one or two orders of magnitude higher than for zinc.

Although they are not necessarily based on rate measurements it seems appropriate finally to mention here the theoretically infinitely low limits of detection afforded by *catalytic amplification.*[202,203] Lowry's recent provocative paper[203]

*Nomenclature and presentation of results in kinetic-based determinations is the province of Project 3.5, Commission V.3, of the International Union of Pure and Applied Chemistry [*Anal. Chem.*, 46, 225A (1974)].

nicely describes the potential of *enzymic cycling* applied to the determination of chemical species in living materials. Enzymic cycling coupled with special manipulative techniques has allowed the determination of NAD (nicotine adenine dinucleotide) in single nerve-cell nuclei in the 10^{-16}-mol range as well as that of the activity of single molecules of glucose 6-phosphate dehydrogenase.[203] One point which seems to be too little emphasized is the care needed in preparing, storing, and dispensing solutions when working with the low concentrations common in some catalytic determinations. This essential care extends to the control of the environment in which analyses are performed and the adoption of special cleaning and rinsing procedures for glassware to be used with concentrations below 10^{-7} *M*. Indeed, the metal content in reagents, such as mineral acids, or in the water used for preparation of standards and other solutions, imposes a practical limit of detection. It is sometimes surprising to see published values of threshold sensitivities (limits of detection) lower than the levels that would be expected from contamination in the water used. The determination of copper at the 10^{-8}-*M* level, for instance, requires water of very high purity. Even triply distilled water from all-borosilicate stills would probably contain copper at a concentration of 10^{-8} *M*.[199] The use of ion-exchange resins alone, although recommended for diminishing heavy-metal contamination, may introduce reducing species which may interfere in some redox systems.[200] A combination of ion exchange and double distillation from an all-borosilicate glass still (fused silica is even better) appears to decrease metal-ion contamination sufficiently and provide water of reasonable purity for most catalytic determinations. Storage in polyethylene bottles may cause contamination from plasticizers which will absorb in the UV region and also may act as reducing agents. A recent report on the extent of contamination of distilled water with free and bound amino acids and microbes[201] describes ways of purifying water and 6 *M* HCl so that these are suitable for determination of amino acids at, or even below, the 10^{-9}-*M* level in biological samples, rocks, lunar soil, meteorites, etc. The overall care necessary, of course, varies depending on the determination at hand. A good example of this is the recommendations and precautions indicated in the determination of zinc at the nanogram level.[197] In this case, plastic ware is preferred to glass, since interference from low concentrations of organic species is of no consequence.

III. DIFFERENTIAL RATE METHODS

A. Introduction

This part of the review is devoted to the simultaneous determination of two or more chemical species by what are called differential reaction-rate methods. The use of the word *differential* has no mathematical connotation here and only implies the *possibility of differentiating chemical species (via rate measurements) without prior separation.* Determinations based on processes other than chemical reactions, such as radioactive decay or mass transfer, have not been included in this review.

In contrast with catalytically based methods, differential rate determinations are not aimed primarily at determining low concentrations of materials in solution but at exploiting differences in rates of reaction of closely related species in mixtures. Most of these reactions are uncatalyzed.

Difficult as it is to establish historical priorities, one of the earliest uses of differential rates with analytical aims appears to have been made by van der Corput and Backer.[204] They used the different velocities of oxidation of two stereoisomeric diols by lead tetracetate or lead tetrapropionate to verify other analytical data.

Differential methods fall in two categories depending on the approach used: (a) those based on *graphical computations*, and (b) those based on *mathematical computation*. Each approach, however, has part of the nature of the other, and in some cases the classification must be based on which one predominates. Table 12 outlines various computational procedures for simultaneous determinations by differential rates. The reader is referred to Chapters 5, 6, and 7 in the monograph by Mark and Rechnitz for more details.[13] Although intuitive thinking may lead the practicing chemist to approximately the same conclusions, the material covered in Chapter 7 (written with the assistance of L. J. Papa) is highly recommended reading. It presents a detailed mathematical evaluation of the *graphical extrapolation method*, the *method of proportional equations*, and of *first-order and pseudo-first-order methods in which the concentration of the species*

TABLE 12

Computational Approaches in Differential Rate Methods

A. Chemical basis of differential rate methods – In the simplest case, that of a binary mixture, a differential rate determination is based in two simultaneous competitive reactions involving the same reagent but occurring at different rates:

$$X + R \rightarrow P$$

$$Y + R \rightarrow P'$$

in which X and Y are the species being determined, R is the common reagent, and P and P' are the respective products.

Method	Conditions under which method is applicable	Basic mathematical expression(s), additional comments
B. Graphical methods		
First-order logarithmic extrapolation	$[R]_0 >> [X]_0 + [Y]_0$	If k_X/k_Y (with k referring to the pseudo-first-order rate constants) is sufficiently large, at a given time, t, $[X]_t \simeq 0$. The logarithmic form of the integrated rate expressions then becomes: $ln\ ([X]_t + [Y]_t) = ln\ [Y]_0 - k_T t$ and $[Y]_0$ can be estimated from the intercept of a plot of $ln\ ([X]_t + [Y]_t)$ against t. The sum of $[X]_0$ and $[Y]_0$ must be known from an independent measurement and $[X]_0$ is calculated by difference. Common practice is to determine one component from the intercept and the other indirectly by difference.
Second-order logarithmic extrapolation	$[R]_0 \leq [X]_0 + [Y]_0$	Integration of the rate equation yields $kt = \frac{1}{[R]_0 - [M]_0}\ ln\ \frac{[R]_0 - x}{[M]_0 - x} - K$ in which k = second-order rate constant, K = constant, $[M]_0 = [X]_0 + [Y]_0$, and x = decrease in [M] at time t. The plot of logarithmic term against time yields a curve with two linear segments. Extrapolation of the second portion to zero time gives K, which can be used to calculate $[X]_0$ from: $K = ln\ \frac{[R]_0 - [X]_0}{[M]_0 - [X]_0}$

TABLE 12 (Continued)

Computational Approaches in Differential Rate Methods

Method	Conditions under which method is applicable	Basic mathematical expression(s), additional comments
		The value of $[M]_0$ must be determined from measurements at $t = \infty$, or by independent measurement. $[Y]_0$ is determined by difference. Alternative ways to estimate the initial concentrations of X and Y can be found in Mark and Rechnitz.[13]
Method of Roberts and Regan[207]	$[R]_0 << [X]_0 + [Y]_0$ (Reaction pseudo-first-order with respect to R)	Solutions of pure X and Y are used to estimate k_X and k_Y and $[M]_0$ is estimated by independent measurement. The initial concentration of sought-for species is then calculated from: $f_X = \frac{(\kappa - k_Y)}{(k_X - k_Y)}$ in which f_X is the mole fraction of X and $\kappa = k_X[X]_0 + k_Y[Y]_0$.
Method of Roberts and Regan modified by Reilley and Papa[208]		Integration of the corresponding rate equation, appropriate substitutions, and rearrangements give: $f_X = \frac{ln([R]_t/[R]_0)}{t[M]_0(k_Y - k_X)} + \frac{k_Y}{k_Y - k_X}$ A plot of $1/t[M]_0$ against f_X at a predetermined value of $[R]_t/[R]_0$ yields a straight line with intercepts corresponding to $1/t[Y]_0$ and $1/t[X]_0$ when f_X equals zero and one, respectively. Minimum errors occur if t is chosen so that $[R]_t/[R]_0 = 1/e$. The plot serves as a calibration curve and is constructed with solutions containing pure X and pure Y; it can be used even if not linear.

TABLE 12 (Continued)

Computational Approaches in Differential Rate Methods

Method	Conditions under which method is applicable	Basic mathematical expression(s), additional comments
First-order single-point method of Kolthoff and Lee[209a]*		Integration and rearrangement of the rate expression yields: $\frac{[X]_t + [Y]_t}{[X]_0 + [Y]_0} = f_X \{\exp(-k_X t) - \exp(-k_Y t)\} + \exp(-k_Y t)$ A plot of the left-hand term against f_X gives a straight line with intercepts of $\exp(-k_Y t)$ and $\exp(-k_X t)$ when f_X equals zero and one respectively. The optimum time for measurement is given by $[1/k_X - k_Y)]ln(k_X/k_Y)$. Papa et al.[219] modified the preparation of the calibration curve by plotting the fraction of reactant having reacted at time t vs. f_X. The intercepts are then $1 - \exp(-k_Y t)$ and $1 - \exp(-k_X t)$ when f_X equals zero and one respectively.
Second-order single-point method of Lee and Kolthoff[209a]	$[R]_0 = [X]_0 + [Y]_0$	To resolve mixtures, the quantities $[X]_t + [Y]_t$ and $[X]_0 + [Y]_0$ are determined. The value of $\%[X]_0$ is read, for instance, from a working curve of $\%([X]_t + [Y]_t)$ vs. $\%[X]_0$. $\%[Y]_0$ is determined by difference.
Linear extrapolation method of Reilley and Papa[208]	$[R]_0 = [X]_0 + [Y]_0$	After component X has reacted completely the following is valid $x = k_Y[Y]_0([R]_0 - x)t + [X]_0$ in which x equals the decrease in [M] at time t. A plot of x against $([R]_0 - x)t$ gives a straight line with intercept equal to $[X]_0$. The value of $[Y]_0$ is obtained by difference. This method can be modified to a single-point type by substitution of $[Y]_0 = [R]_0 - [X]_0$ in the equation to obtain: $[X]_0 = \frac{\{x - k_Y([R]_0 - x)t[R]_0\}}{\{1 - k_Y([R]_0 - x)t\}}$

*This work of Kolthoff and Lee is historically of great significance since it stimulated interest in reaction rate methods.

TABLE 12 (Continued)

Computational Approaches in Differential Rate Methods

Method	Conditions under which method is applicable	Basic mathematical expression(s), additional comments
		since once the value for k_Y and $[R]_0$ have been obtained, a single measurement of x allows the estimation of $[X]_0$.
Method of fractional-order kinetics[211]		If Y is the slower-reacting component the order of the reaction, n, with respect to it is determined. After reaction of X is completed, the following applies: $(n-1)k_Y t = (1/[Y]_t^{n-1}) - (1/[Y]_0^{n-1})$ $[Y]_0$ is then determined from a plot of the first term on the right-hand side of the equation against t. $[X]_0$ is determined by difference from independent knowledge of $[X]_0 + [Y]_0$.
Logarithmic extrapolation for mixtures reacting by mixed higher stoichiometries[212]	Recommended only for mixtures containing more than 30% of the faster-reacting component	Nonempirical procedure without use of calibration curves. Each component has a high (different) stoichiometry with reagent R. Independent knowledge of $[X]_0 + [Y]_0$ is not needed. When all the faster reacting component, X, has disappeared, a plot of $ln \frac{[R]_0 - x_R}{[Y]_0 - x_Y} = L$ against t can be made and the quantity $ln\, i = \frac{L_1 t_2 - L_2 t_1}{t_2 - t_1}$ can be estimated from the plot at times t_1 and t_2. A knowledge of i allows determination of X in the mixture from $\%X = \frac{100 M_X}{W} \cdot \left\{\frac{W \cdot i - [R]_0 M_Y}{M_X \cdot i - x M_Y}\right\}$

TABLE 12 (Continued)

Computational Approaches in Differential Rate Methods

Method	Conditions under which method is applicable	Basic mathematical expression(s), additional comments
		in which M stands for the correponding molecular weights, W is the total initial weight of the mixture, and x is the ratio of moles of reagent to moles of component for reactant X. %Y is obtained by difference.
Graphical derivative and graphical integral methods[213]		Resolution is achieved by evaluation of the second-order differential rate laws and the second-order integral.
C. Methods based on mathematical computations		
Method of Roberts and Regan modified by Mark and Greinke[214]		The total concentration of reactions must be determined by an independent method. From the decrease of R with time, κ can be estimated from the expression $ln\ ([R]_t/[R]_0) = \kappa t$ $[X]_0$ is then calculated from the solution of two simultaneous equations $\kappa = k_X[X]_0 + k_y[Y]_0$, and $[M]_0 = [X]_0 + [Y]_0$ The value of $[Y]_0$ is determined by difference.
Double-point method of Reilley and Papa[208]		A modification of the linear extrapolation method which operates under the same experimental conditions. The value of $[X]_0$ is obtained from

TABLE 12 (Continued)

Computational Approaches in Differential Rate Methods

Method	Conditions under which method is applicable	Basic mathematical expression(s), additional comments
		$$[X]_o = \frac{\left\{x - \frac{([R]_o - x)\,t}{([R]_o - x')t'} \cdot x'\right\}}{\left\{1 - \frac{([R]_o - x)\,t}{([R]_o - x')t'}\right\}}$$ in which x and x' are the concentrations of M reacted at times t and t'. Both times are selected after all X has reacted.
Method of proportional equations	$[R] >> [X]_o + [Y]_o$ (Pseudo-first-order kinetics with respect to X and Y).	Initial reactant concentrations are obtained by solving at least two linear simultaneous equations such as: $[\Pi]_a = [X]_o K_{Xa} + [Y]_o K_{Ya}$ $[\Pi]_b = [X]_o K_{Xb} + [Y]_o K_{Yb}$ in which Π is any measurable parameter; a and b stand for two different independent measured values of an additive variable proportional to the concentrations of reactants. Almost any experimental variable can be used provided that $K_{Xa}K_{Yb} \neq K_{Xb}K_{Ya}$. The optimum conditions, however, are when $K_{Xa}/K_{Ya} > 1$ at one condition but is less than one at the other. Theoretically, any number m of chemical species can be determined by this approach provided that at least m adequate simultaneous equations can be formulated and solved.

sought is much smaller than that of the reagent. Useful insight into differential rate determinations can also be gained from two rather recent Ph.D. dissertations.[205,206]

B. An Evaluation of Selected Differential Rate Methods for the Simultaneous Determination of Closely Related Species

This evaluation covers the commonest differential rate methods and is based in part on Chapter II in Ellis' thesis.[206] On the basis of flexibility and adaptability, the following general methods can be distinguished: *(a) the logarithmic graphical extrapolation methods* (both first- and second-order), *(b) the method of Roberts and Regan, (c) the method of proportional equations,* and *(d) the single-point method for first-order reactions developed by Lee and Kolthoff.* Most other methods can be used only under very special conditions, and some are described in only one literature report.

Table 13 summarizes the advantages and disadvantages of the four general methods above. Tables 12 and 13, in conjunction with Figure 7 in

TABLE 13

An Evaluation of Some Selected Differential Rate Methods

A. Graphical extrapolation methods – These were the first differential rate methods to be widely used and are most frequently mentioned in the total literature.

Advantages	Disadvantages
1. Since these methods depend on plotting the logarithm of the total reactant concentration against time, there is no need to determine rate constants.	1. Component X (the faster-reacting) must be about 99% consumed before useful data can be obtained.
2. Temperature is not a critical variable.	2. The total initial concentration of reactants must be known. Its determination often requires following the reaction to completion.
3. The plotting procedure usually minimizes small errors since the "best" straight line is drawn through several points.	3. If continuous monitoring of the reaction is not possible, a rather large number of samples have to be withdrawn from the mixture to follow the progress of the reaction.
4. Since the methods are not restricted to constant processes following first-order kinetics, they can be applied in some cases in which synergism is observed.[215]	
5. The first-order method can be used for the determination of three components in a mixture.	

B. Method of proportional equations – The most flexible approach to reaction rate determination of closely related components in mixtures. Even though its application is rather recent, it is now more frequently used.

Advantages	Disadvantages
1. Requires generally shorter times than the other approaches.	1. The monitored property must be additive; hence the method is not applicable in case of synergism.
2. Even if the mixture reacts by complex kinetics, it can be applied if the proportionality constants can be determined.	2. Rate constants must be carefully measured.

TABLE 13 (Continued)

An Evaluation of Some Selected Differential Rate Methods

Advantages	Disadvantages
3. *A priori* knowledge of the total initial concentration of reactants is not required.	
4. Values of ratios of rate constants $\cong 4$ suffice.	
5. Easily adaptable to automation, being ideal for fast reactions and for initial-rate methods.	
6. Readily adaptable to the determination of more than two components in a mixture. Preferably used in combination with a minicomputer since the formulation and solution of the necessary simultaneous equations is then a simple task.	

C. The method of Roberts and Regan

Advantages	Disadvantages
1. Small ratios of k_X/k_Y can be tolerated. In a mixture containing 2.5% of X with $k_X/k_Y = 2.2$, for instance, X was determined with only 2 to 3% error.[209]	1. The method is restricted to binary determinations.
2. Since $[R]_0 << [X]_0 + [Y]_0$, side reactions are minimized.	2. The sum of the initial concentrations of the reactants must be independently determined.
3. Useful over a wide range of $[X]_0/[Y]_0$ as long as $k_X[X]_0$ is about 5% the value of κ.	3. Useful only when it is possible to follow the concentration of reagent, R, or of a common product of the two competitive reactions.
4. The large concentration of reactants can increase the rate of very slow reactions and make them useful for determination. This, of course, may also make some reactions too fast to be of use.*	

*The classification of a reaction as *fast* or *slow* is relative to the mixing and detecting capabilities available. The literature contains statements that rates of reactions with half-lives of less than 10 sec are difficult to measure with acceptable accuracy with average laboratory facilities. On the other hand, some practicing analysts using stopped-flow techniques consider that only reactions occurring in less than a few milliseconds are too fast to be useful. Also the rejection of a given reaction because it is considered too slow is relative to what other means are available for the determination of the species in question. Those interested in utilization of very fast reactions are referred to a recent paper by Lin and Rorabacher[216] in which the authors describe a mathematical approach to stopped-flow kinetics of very fast second-order reactions. With this approach, second-order rate constants of $7 \times 10^6\ M^{-1}\ sec^{-1}$ were determined even where the calculated reaction half-life was 700 μs in comparison with a rated instrumental dead time of 5 ms.

TABLE 13 (Continued)

An Evaluation of Some Selected Differential Rate Methods

D. First-order single-point method – Like the MPE, this method is based on the constant fractional life concept.

Advantages	Disadvantages
1. Applicable to nearly any reaction mechanism by using empirical calibration curves.	1. Requires ratios of rate constants of 4:1 or larger.
	2. The total initial concentration of reactants must be determined independently.
	3. Limited to binary determinations.

TABLE 14

Experimental Variables Utilized to Formulate Simultaneous Equations in the Method of Proportional Equations (including typical references)

*Time[217-221]
*Solvent(s)[222]
*Temperature[223]
*Concentrations of catalyst (enzyme)[224]
*Reacting conditions[225]
*Physico-chemical characteristics of the components[200,226]

Mark et al.[16] (The same Figure appears in Mark and Rechnitz (Reference 13, p. 79) and in Guilbault (Reference 32e, p. 186)) and should prove useful in selecting the approach to use under given circumstances.

Examination of Table 13 shows that the method of proportional equations, MPE, when applicable, is the best choice available to the analyst. As stated in the table, almost any experimental variable or situation can be utilized to formulate the simultaneous equations to be used for resolution of the several components simultaneously determined. Table 14 gives a summary of this matter.

Two factors can be singled out as predominant in recent applications of the MPE: the use of metal(ligand)-exchange reactions and the use of digital computers for the processing of data. The rapid nature of exchange reactions requires the application of stopped-flow techniques, and the use of computers allows simultaneous determinations of n species by use of a number of measurements, m, such that $m >> n$. It has been reported, in resolving binary and ternary mixtures of alkaline earth metals, that a linear least-squares treatment of 200 data points, taken at regularly spaced time intervals,[9c] yielded precision and accuracy which were 5 to 10 times those obtained when 30 points were used in similar fashion.[9a]

In a multicomponent mixture, Margerum et al.[9b] reported the determination of Mg, Zn, Mn(II), Cd, Hg(II), and Co(II) in the presence of Fe(III) and Ni(II) also. These latter ions reacted too slowly to be measured. The accuracy of these determinations was about 10%; four sets of conditions attained by changing pH and time-scan were employed.

Although much more useful than many reported catalytic determinations, differential rate determinations are comparatively scarce in the literature. This reflects the fact that conditions for determining more than one species simultaneously are difficult to design without a large amount of empirical work. Moreover, "indicator reactions" for single-species determination (particularly in redox reactions) provide an almost endless list of new systems.

C. Recent and Typical Applications

Table 15 is a summary of typical and recent

TABLE 15

Recent and Typical Applications of Differential Rate Methods

A. Applications of logarithmic extrapolation procedures

Species determined	Author(s), reference, comments
Iodate–bromate ions; periodate–bromate ions; and dichromate–bromate ions	Hanna and Siggia[227] – This paper demonstrates the applicability of a flow method to differential kinetic determinations. The procedure is illustrated by reactions which liberate iodine.
Methyl acetate–isopropyl acetate	Papoff and Zambonin[228] – Kinetic differential determinations in a "model" system based on the alkaline hydrolysis of the esters and aimed at testing a quasi-adiabatic enthalpimetric (thermometric) method. Relative errors ranged from ±0.6% to 4% for methyl acetate in mixtures containing 49.7 and 39.7% respectively. Relative errors for isopropyl acetate were between ±1.3 and ±2%.
Ytterbium-prasecdymium and lanthanum–samarium	Budarin et al.[229] – Determination based on differences in the rate of ligand exchange between EDTA and the colored complexes of the rare earth with Xylenol Orange. Reaction monitoring by stopped-flow spectrophotometry. In general, the results show about 15% error for a single determination.
Nitric oxide–nitrogen dioxide	Coetzee et al.[230] – Determination based on the formation of the nitrosyl iron(II) ("brown-ring") complex in sulfolane containing 1.6 volume % of water. The method is relatively free from interferences. Reaction was pseudo-first-order with respect to the reactants. Logarithmic extrapolation of conventionally recorded spectrophotometric data was used to determine NO_2 (NO obtained by difference). A stopped-flow technique is also reported for the determination of NO (in this case NO_2 is determined by difference from the limiting absorbance value, which is closely approached 4–5 min after the reaction has been started).
Formic acid–tartaric acid	Berka and Korečková[231] – Determination based on differences in the rate of oxidation with permanganate ion. Reactions were quenched by addition of Mn(II). The hydrated MnO_2(s) formed was converted to the pyrophosphate complex of Mn(IV) and potentiometrically titrated with standard hydroquinone solution. In a mixture containing 12.7 weight % formic acid, tartaric acid was determined with 0.5% error and formic acid with 3.2% error. Equal errors of 1.4% were observed in a mixture of equal weights of each component. A mixture containing 81.8 weight % formic acid gave an error of 19.8% for formic acid and 89% for tartaric acid.

TABLE 15 (Continued)

Recent and Typical Applications of Differential Rate Methods

Species determined	Author(s), reference, comments
B. Method of proportional equations*	
Mixture of five organic peroxides (two peroxycarboxylic acids, two diacyl peroxides, and a hydroperoxide)	Hawk et al.[226] – The authors have used a variety of reaction conditions which coupled with computer evaluation of five linear equations with five unknowns allowed determinations of as low as 0.002 milliequivalent of individual peroxide/ml with a relative error less than 12%.
Ternary mixtures of dysprosium, holmium, and ytterbium	Yatsimirskii et al.[221] – Stopped-flow spectrophotometry of ligand exchange between EDTA and the colored complexes of the rare earths with Xylenol Orange. Discriminating variable: time.
Binary and ternary mixtures of sulfonephthalein dyes (Cresol Red–Cresol Purple, Cresol Red–Phenol Red, Cresol Red–Cresol Purple–Phenol Red)	Ellis and Mottola[200] – Kinetic determinations based on the selective oxidation of the dyes by periodate ion (pH 7–10) catalyzed by Mn(II). Differentiation of the reaction rates in dye mixtures was accomplished by altering one or more experimental conditions, namely, the manganese(II) concentration, the pH, the wavelength, and the analytical time interval. The kinetic procedures compared well with spectrophotometric measurements at equilibrium also based on MPE, and show an advantage in the case of an unreactive absorbing background.
C. Miscellaneous Approaches	
Lanthanum–neodymium	Worthington and Pardue[232] – Description and application of an analog system for automatic graphical presentation of simultaneous kinetic determinations. Results are extracted from graphical extrapolation of plot of product concentration against exponential functions. Quantitative determinations down to the 10^{-5}-*M* level with relative errors of 0.3 to 16% are reported. The reactions used involve the exchange of Cu(II) and rare earth complexes with CDTA.

*The differential determination of 2-ketohexoses (fructose, tagatose, and psicose) by their reaction with cysteine in sulfuric acid has been proposed using simultaneous equations [Bissett, D. L., Hanson, T. E., and Anderson, R. L., *Microchem. J.*, 19, 71 (1974)]. The authors, however, did not pursue it because in their specific work mixtures of these compounds are not encountered.

TABLE 15 (Continued)

Recent and Typical Applications of Differential Rate Methods

Species determined	Author(s), reference, comments
Mixtures of aminopoly-carboxylic acids (NTA-EDDA, NTA-EDDA-EGTA)	Coombs et al.[9e] – On-line regression analysis of stopped-flow spectrophotometric data. Procedure based on the large differences induced in the rate of formation of tetracyanonickelate ion. A four-component mixture (EGTA-HPDTA-HEEDTA-EDTA) was also analyzed but with off-line computation.
Propanal–cyclohexanone	de Oliveira and Meites[233] – Differential technique applied to thermometric measurements. Based on reaction of the carbonyl compounds with excess hydroxylamine. Details of this approach are given in the text.
Several binary mixtures of olefins in monomer and polymer composition	Kreshkov et al.[234] – Determination based on reactivity of double bonds toward mercury(II) acetate in methanol. Plots of amounts of $Hg(OAc)_2$, used up in methoxymercuration, against time showed two distinct segments if rates differed by two orders of magnitude or more.
Germanium(IV)–silicon(IV)	Yonekubo et al.[235] – Determination based on the reduction of heteropoly acids. Under specified conditions the initial rate of formation of germanomolybdenum blue was much smaller than that of silicomolybdenum blue. The following equations were used for the determination in mixtures: $[Ge]_0$ (μg/ml) = $-2.31\ v_0 + 7.20\ A$ $[Si]_0$ (μg/ml) = $1.47\ v_0 - 0.58\ A$ in which v_0 = initial rate of molybdenum blue formation in absorbance units, and A = final absorbance of the reacting solution at 700 nm. Relative errors ranged from 6 to 25%.
Niobium–tantalum	Alekseeva et al.[236] – Determination on the basis of the catalytic action of Nb(V) and Ta(V) on the $I^- + H_2O_2$ (starch) indicator reaction at pH 1.1. Niobium rapidly loses its catalytic activity (few minutes) whereas tantalum activity is retained for many days. Relative errors of 8% are reported for determinations of 1×10^{-5} g of the metals.

plications of differential rate determinations. It hoped that material for an expanded table will plentifully available in years to come.

The relative magnitudes of rate constants are of pital importance in selecting the treatment and proach in a given case.[13] This is brought up ain in the work of Budarin et al.[229] on the termination of ytterbium and praseodymium in ixtures and of lanthanum and samarium. In the se of Yb and Pr, $k_X/k_Y \geqslant 3$, and the ncentration of the slower-reacting component is determined from plots of log A_t vs. t (A = sorbance), and extrapolation to $t = 0$. In the se of lanthanum and samarium, however, k_X/k_Y 3, and concentrations were estimated from plots K* vs. mole fractions (K* = slope of the initial raight-line portion of log A_t against t).

Digital computers play an increasing role in ndling data for differential rate determinaons.[6,9,233] This approach to data handling is egantly described by Gardiner:[237] *"Brute force ay not have the aesthetic appeal of mathematical sight, but it can be effective where insight fails. he brute force in question here is the digital mputer."* From an analytical viewpoint, this proach offers two advantages: (a) less experiental work is required to seek discriminating riables, and (b) use of a large number of data oints greatly minimizes errors.[9c] The work of de liveira and Meites,[233] based on the simultaneous valuation of four parameters in a single equation, an example. Although the chemical system osen by the authors afforded a ratio of k-values only about 4, and although they had to resort heat corrections (since thermometric onitoring was employed),* the maximum relave errors were only approximately 12% in a ixture of 9 mole % propanal and 91 mole % clohexanone, and 10.3% in a mixture of 75 ole % propanal and 25 mole % cyclohexanone. s an additional feature, the rate constants in ixtures differed from those for the individual mpounds in pure solutions, illustrating deviaons from additive behavior in mixtures. Thus, the nergistic effect observed by Siggia and anna[238] was confirmed and traced to the fact at the value of k for cyclohexanone in the mixture is 30% larger than the value of k for the same compound in pure solutions. No significant difference between the values for propanal alone and in mixtures was observed.

The approach of de Oliveira and Meites has, as its starting point, the general procedure of Meites et al.[239] By utilizing a general non-linear least-squares computer program, the two parameters ΔT^* and ϵ are estimated from the equation $\Delta T = \Delta T^* \exp[-\epsilon(t - t^*)]$, in which ΔT^* represents the change in temperature at an arbitrarily chosen time t^* after the initiation of the reaction. The value of ϵ is then used in computing the best values of the four unknown parameters in the expression:

$$\Delta T = \frac{k_X(\Delta T_{X,\,corr.,\,\infty})[\exp(-k_X t) - \exp(-\epsilon t)]}{\epsilon - k_X} + \frac{k_Y(\Delta T_{Y,\,corr.,\,\infty})[\exp(-k_Y t) - \exp(-\epsilon t)]}{\epsilon - k_Y} + \xi.$$

in which ξ is a correction term. It is needed because of a small contribution to ΔT by some prior reaction which occurs almost instantaneously on mixing either propanol or cyclohexanone with hydroxylamine, and is defined by

$$\xi = (\Delta T_\infty - \Delta T_{X,corr.,\infty} - \Delta T_{Y,corr.,\infty})$$

with $\Delta T_{corr.,\infty}$ being the overall change in temperature (in the absence of heat exchange) contributed by the corresponding individual compounds, and ΔT_∞ being the limiting value obtained by numerical evaluation of $\Sigma\Delta T + \int_0^t \epsilon(\Delta T)dt$, i.e., $\Delta T_\infty = (\Delta T_X^\circ - \Delta T_Y^\circ) - \Delta T_{X,corr.,\infty} + \Delta T_{Y,corr.,\infty}$. The values of $\Delta T_{X,corr.,\infty}$ and $\Delta T_{Y,corr.,\infty}$ are directly proportional to $[X]_0$ and $[Y]_0$, respectively. Average values of the corresponding proportionality constants were estimated with mixtures or from data obtained with the pure compounds. These values were then used to compute the concentrations of individual components in the "unknown" mixtures.

Applications of thermometric kinetic procedures to the analysis of binary mixtures of organic compounds have been iscussed briefly and demonstrated recently [Vajgand, V. J., Gaal, F. F., Zrnic-Zeremski, Lj. P., and Soros, V. I., *Therm. nal. Proc. Int. Conf. 3rd.*, 2, 437, 1971; Wiedemann, H. G., Ed., Birkhaeuser, Basel, Switzerland; *Chem. Abstr.*, 78, 43488m (1973)].

Also worth noticing is the rather simple analog system reported by Worthington and Pardue[232] which is offered in the recognition that *"while the digital computer has proved to be a powerful tool . . ., it is probable that situations will exist in which it is not possible to dedicate a digital computer to this type of problem, and simpler, less expensive instrumentation will be desired."* The reported system greatly simplified both data collection and processing steps in differential rate determinations.

Not included in Table 15 but of singular value is the recent contribution of Kloosterboer[240] offering a continuous pH-variation method for the differential determination of cations based on the chemical systems described by Margerum et al.[9a,9b] Kloosterboer uses a continuously decreasing pH instead of fixed pH-values. For a mixture, the absorbance of the copper complex with CDTA as a function of time then appears as a series of superposed S-shaped curves. If rate constants differ by more than two orders of magnitude, the individual contributions are easily resolved. Smaller differences in rate constants demand the use of a computer. Kloosterboer's modification requires no stopped-flow apparatus and seems easily adaptable to automated instrumentation for routine determinations.

IV. CLOSING REMARKS

As measurements in chemical systems not at equilibrium and rates of chemical reactions are both more frequently used in analytical chemistry, this review has first attempted to present the converging reasons for this attitude. The main purpose of this paper is, however, to set forth the present status in the areas of catalytic and differential rate determinations, with focus on the most recent developments. Considerable use of tabulations is made in the conviction that it stresses salient points and conveys a perspective which may become diluted in textual discussion. To minimize duplication of the already abundant literature on the subject those aspects considered of importance (both positive and negative) are organized and underlined rather than offering an assembly of data.

Acknowledgments

The author is grateful to the National Science Foundation for support (Grant No. GP-38822X) that made this review possible. Appreciation is also expressed to Otis C. Dermer and V. V. S. Eswara Dutt for reading the manuscript, and to those who facilitated the author's work by providing reprints or preprints.

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