Acid-Base Titrations in NONAQUEOUS SOLVENTS

By
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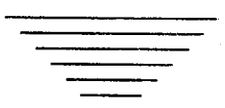

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INTRODUCTORY COMMENTARY

Industrial analytical chemists are constantly seeking simple, fast and accurate methods to reduce the cost of control in chemical processes. More and more continuous processes are being put into operation and these require a rapid evaluation of the several steps. Part of this evaluation is made by continuous reading and recording instruments such as flow meters, pH meters, refractometers and viscosimeters. These continuous reading and recording instruments are not able to give sufficient information for accurate control of many processes. It is then necessary to withdraw samples for analysis by instrumental or chemical means. The use of instruments to analyze withdrawn samples is often expensive and time consuming. Such instruments as the mass spectrometer and the infrared spectrometer are serving a very useful need in the chemical industry but do have a high initial cost and require highly trained personnel for operation. Moreover, their accuracy is often not really sufficient.

Acid-base titrations in nonaqueous solvents possess the basic requirements for good analytical methods of accuracy, speed and simplicity. These are primary requirements in a control laboratory and for specification analyses. Recently developed acid-base titrations in nonaqueous solvents have given the production control chemist a much wider use for the simple, direct acid-base titrations which may be carried out conveniently either with indicators or potentiometrically. At the present time, procedures are available for bases, salts and H-acids but the work of Luder and co-workers at Northeastern University shows promise of extending the applications to titration with other acids such as boron trichloride and antimony trichloride.

The present applications are particularly striking in the pharmaceutical industry. Many pharmaceuticals contain an amine or pyridine group which is readily titrated in nonaqueous solvents. Phenols, oxazolines, borates, enols, soaps, aluminates, nitrates, chlorides, silicates and arsenates can be determined by simple, direct titrations. The scope is increasing almost daily. I consider the application of titration in nonaqueous solvents one of the most important developments that has been placed at the disposal of the control chemist.

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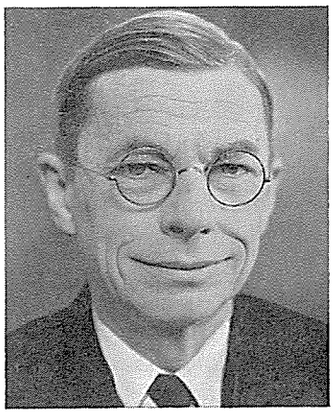
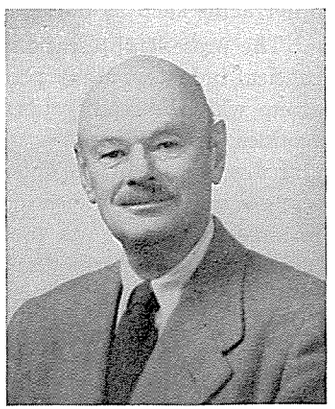


James B. Conant

James S. Fritz



Norris F. Hall

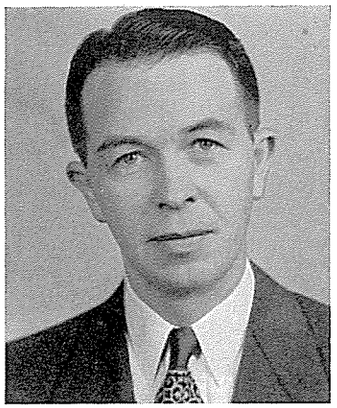
INTRODUCTION

Acid-base titrations represent a general and valuable method for determining organic compounds having pronounced acidic or basic properties. Titration of such compounds in water is limited in scope, however, due to slight solubility and because in many cases their acidic or basic strength is too slight to give a sharp end point. Titration in nonaqueous solvents permits accurate determination of literally hundreds of acids and bases which cannot be titrated satisfactorily in water or alcohol-water mixtures. Good methods are now available for titration of most aromatic, aliphatic and heterocyclic amines as bases and for the titration of carboxylic acids, acid anhydrides, enols, imides and phenols and even alcohols as acids. Many organic and inorganic salts can be titrated, some as acids and others as bases.

Although the history of acid-base titrations in nonaqueous solvents dates back at least fifty years, the bulk of analytical papers on this subject are of quite recent publication. Unlike many recent analytical developments, this method is quite simple and requires no elaborate equipment. Indeed titration in nonaqueous solvents possesses the virtues of an ideal analytical method; speed, accuracy and simplicity of technique and equipment.

Acid-base titrations in either water or nonaqueous media are general and do not ordinarily differentiate between different types of acids or bases. Although a widely applicable method of this type is valuable, it would be useful to make the method more selective in certain instances. This has been accomplished in the analysis of amine mixtures. Tertiary amines can be determined in the presence of primary and secondary amines after acetylation in acetic anhydride-acetic acid solution. Secondary amines can be determined in the presence of primary amines by first treating the mixture with salicylaldehyde.

The purpose of this booklet is to make available in a single source the essential theory and the more useful procedures on nonaqueous acid-base titrations. Because much of the work on this subject is so recent, many details regarding scope and interferences are still missing. Although some refinement and modification may be desirable, the methods given are thoroughly usable in their present form.



Peter C. Markunas

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C. W. Pifer

John A. Riddick

I. ACID BASE THEORIES

Some knowledge of the leading acid-base theories is essential if acid-base behavior in nonaqueous solvents is to be understood.

The Arrhenius theory stressed dissociation into ions. An acid was defined as a compound which ionized in water to give hydrogen ions and a base as one which gave hydroxyl ions. Neutralization always involved the formation of a salt and water. These definitions were widely adopted and are still used by some even though they are totally inadequate for reactions in nonaqueous solvents.

The theory of solvent systems, begun by Franklin in 1905 (*1*) and extended by Germann in 1925 (*2*) is of some importance. It was reasoned that if water ionizes into hydronium and hydroxyl ions,

$$2H_2O = H_3O^+ + OH^-$$

then liquid ammonia must ionize into ammonium and amide ions,

$$2NH_3 = NH_4^+ + NH_2^-.$$

According to this theory, any substance that increases the solvent cation concentration is an acid while any substance that increases the anion concentration is a base. Thus in liquid ammonia, ammonium chloride is an acid comparable in strength to hydrogen chloride in water. In ethanol, sodium ethoxide is a base of about the same strength as sodium hydroxide in water.

Germann assumed that the aprotic solvent, phosgene, ionizes as follows:

$$COCl_2 = COCl^+ + Cl^-.$$

In phosgene, aluminum chloride is an acid because it reacts to increase the solvent cation concentration,

$$AlCl_3 + COCl_2 = COCl^+ + AlCl_4^-.$$

Evidence that aluminum chloride acts as an acid in this case is that this solution dissolves metals and neutralizes certain metallic chlorides.

The theory of solvent systems seems to be fairly satisfactory for ionizable solvents but is not applicable to acid-base reactions in dioxane, benzene and other non-ionizable solvents.

BRONSTED THEORY

An acid is defined as any substance that can give up a proton. A base is any compound or ion that can accept a proton. These definitions lead to the relationship,

$$\text{Acid} = H^+ + \text{Base}.$$

Just as free electrons cannot exist in solution, it has also been calculated that free, uncombined protons also cannot exist in solution. Since this is true, no reaction takes place unless a base is added to accept the proton from the acid. With this in mind, the following expression can be derived:

$$\begin{aligned} A_1 &= H^+ + B_1 \\ B_2 + H^+ &= A_2 \\ \hline A_1 + B_2 &= A_2 + B_1 \end{aligned}$$

It will be noted that this is analogous to adding two redox half reactions to obtain a complete reaction. According to Brønsted, all acid-base reactions take place by an acid reacting with a base to form a new acid and a new base.

One consequence of the Brønsted theory is that acids are not limited to cations nor bases to anions. Thus an acid may be a neutral molecule such as hydrogen chloride, a cation ($C_5H_5NH^+$, H_3O^+, etc.) or an anion (HCO_3^-, $H_2PO_4^-$, etc.). A base may also be neutral (NH_3, C_5H_5N, etc.), an anion (OH^-, $OC_2H_5^-$) or even a cation ($Co[OH][NH_3]_5^{++}$, $Al[OH]_2^+$).

Another important consequence is that the Brønsted theory fits acid-base reactions in nonaqueous solvents as readily as it does those in aqueous solution. For example, the following reactions all follow ($Co[OH][NH_3]_5^{++}$, $Al[OH]_2^+$).

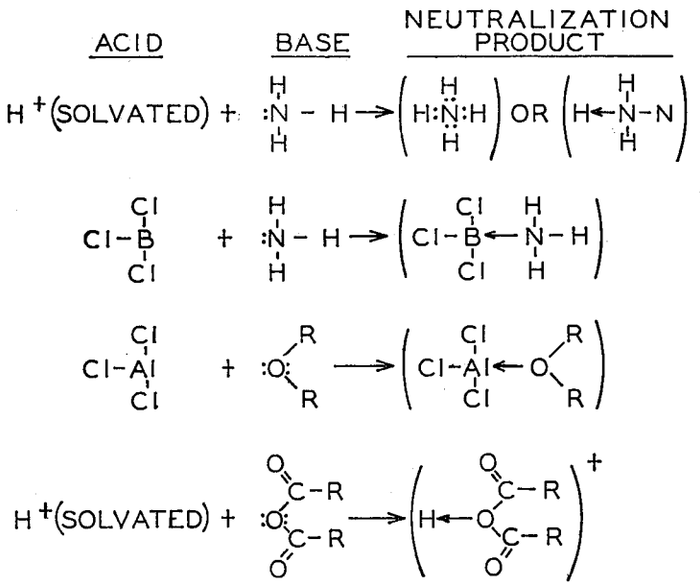
Solvent	Acid + Base → Acid + Base
H_2O	HCO_3^- + OH^- → H_2O + $CO_3^=$
H_2O	HCl + H_2O → H_3O^+ + Cl^-
NH_3	HAc + NH_3 → NH_4^+ + Ac^-
EtOH	NH_4^+ + OEt^- → EtOH + NH_3
ϕH	HPicrate + ϕNH_2 → ϕNH_3^+ + $Picrate^-$

The fact that a substance cannot act as an acid unless a base is present to accept the proton, leads to the prediction that a neutral acid will not be ionized unless the solvent it is dissolved in has some basic properties. Brønsted reported an experiment which confirms this (*3*). A solution of picric acid in benzene is colorless and the conductance is negligible. This shows that in the inert solvent, benzene, picric acid is not ionized. If a solution of aniline in benzene is now added to the picric acid, the solution becomes yellow (due to the formation of picrate ions) and the conductance increases.

G. N. LEWIS THEORY

Lewis defines an acid as an electron pair acceptor and a base as an electron pair donor. The striking part of this theory is that boron

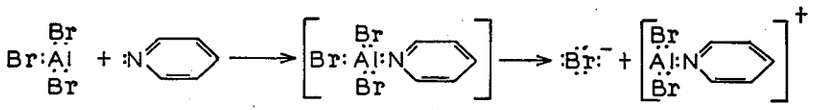
fluoride, aluminum chloride, stannic chloride and several other non-hydrogen containing substances are included as acids. Typical bases are the hydroxyl and alkoxyl ions, amines, ethers and even carboxylic acid anhydrides. Several examples of acid-base reactions as represented by this theory are given below.



Lewis defends his inclusion of boron chloride and similar compounds as acids by pointing out that they have all of the properties commonly associated with acids. For example, in chlorobenzene boron chloride will change crystal violet indicator to the acid color. Addition of a base then returns the indicator to the basic color. Aluminum chloride is a Lewis acid but is insoluble in carbon tetrachloride. Shaking a mixture of aluminum chloride and carbon tetrachloride and filtering gives a clear filtrate which does not give an acid reaction to crystal violet indicator. This indicates that no hydrolysis to hydrogen chloride takes place due to traces of moisture. Addition of crystal violet indicator to a suspension of aluminum chloride in carbon tetrachloride, however, gives an acid reaction due to the acidic nature of the aluminum chloride *molecule*.

In chlorobenzene, amines, ethers, alcohols and carboxylic acid anhydrides convert crystal violet from green to violet showing that each is a base. More alcohol or ether is required to convert crystal violet to its basic color because they are much weaker bases than amines.

According to Lewis, acid-base reactions can be classified either as neutralization or as displacement reactions. Neutralization is defined as the formation of a coordinate covalent bond. The product of neutralization may be a covalent compound, or the formation of a coordinate covalent bond may be followed or be accompanied by ionization so that the product is a salt. The reaction of two covalent compounds, aluminum bromide and pyridine gives a white precipitate with a sufficiently high melting point to indicate that it is a salt. In this case the electrical "strain" produced by the formation of the covalent bond probably results in ionization of one of the bromide atoms (*4*).

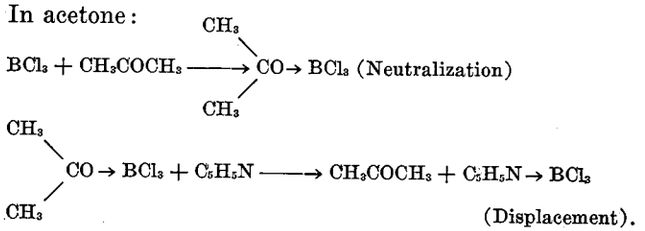


The product of neutralization is not necessarily neutral in the sense that it is neither acidic or basic. In fact, according to this theory hydrogen chloride is merely the neutralization product of a proton and an anion base. Kolthoff (*5*) believes this to be one of the weaknesses of the Lewis theory.

Displacement reactions take place when a stronger acid displaces a weaker acid from combination with a base or when a stronger base liberates a weaker base bound to an acid. The guiding principle in this type of reaction is that a weaker coordinate bond is broken to form a stronger one. The examples given below illustrate this.

1. In water:
   $H_3O^+ + CO_3^= \longrightarrow H_2O + CO_2$
   (The H_3O^+ displaces $O^=$ from combination with the weaker acid, carbon dioxide).

2. In acetone:



3. In water:
   $HCl + H_2O \longrightarrow H_3O^+ + Cl^-$
   (The stronger base, water displaces the weaker base, chloride from combination with the proton).

The G. N. Lewis theory is thoroughly discussed in a book by Luder and Zuffanti (*4*).

II. ACID-BASE BEHAVIOR IN NONAQUEOUS SOLVENTS

SPEED OF REACTIONS

Unlike redox reactions, which proceed with measurable velocity, most acid-base reactions occur almost instantaneously. Lewis and Seaborg (*6*) noted that acids such as hydrogen chloride and boron chloride react instantly with certain indicator bases even at —70° C. Several compounds were found which behaved like typical acids and bases except that they reacted slowly especially at low temperatures. These substances were termed "secondary" acids and bases. The explanation for their behavior appears to be that they are only acids or bases after they have undergone certain electron shifts or other structural transformations requiring activation energy. This concept is useful in explaining why some indicator acids and bases respond rapidly while others are only slowly reversible.

IONIZATION

The extent to which salts dissociate depends primarily on the dielectric constant of the solvent. With acids (or bases) however, the basicity (or acidity) of the solvent also becomes important. As the basic strength of a solvent increases, so will the tendency for an acid to react with the solvent increase. In a solvent possessing some basic properties and having a high dielectric constant, a strong acid such as hydrogen chloride will be highly ionized. If the solvent has some basic properties but has a very low dielectric constant (dioxane, for example), a strong acid will merely react with the solvent to form "ion pairs."

Solvents may be divided into three classes:

1. Ionizable. Examples of this type are water, alcohol, liquid sulfur dioxide, acetic acid and phosgene. Both acids and bases react with the solvents in this group to increase either the solvent cation or anion concentration.

2. Nonionizable, but react with acids or bases (usually not with both). Examples are ether, dioxane and pyridine.

3. Inert. Typical solvents of this type are benzene and carbon tetrachloride. Since neither acids or bases react with the solvent, no ionization is likely to occur.

It should be emphasized that ionization of an acid is not required for a successful titration with a standard base. In 1912, Folin and Flanders (*7*) used conductivity measurements to show that solutions of carboxylic acids in benzene were essentially non-ionized, but could

nevertheless be titrated quantitatively with sodium ethoxide. Very sharp end points were obtained using phenolphthalein indicator. When increasing amounts of alcohol were added to the original solution, the conductance increased but the end points became less sharp.

The basic strength of a solvent is one of the most important factors governing the reaction of an acid with a basic titrant. Solvents with greater basic strength hold on to an acid more firmly and require a stronger base to remove the acid from combination with the solvent. Similar considerations apply to bases in acidic solvents.

LEVELING EFFECT

In solvents possessing some basic strength the strongest acid that can exist is the solvated proton. Thus both perchloric and hydrochloric acids are partially neutralized by the basic solvent, water, to form the hydronium ion. Inherently, perchloric acid is a stronger acid than hydrochloric but both are sufficiently strong to react completely with water, the same acid (H_3O^+) resulting in either case.

$$HClO_4 + H_2O \longrightarrow H_3O^+ + ClO_4^-$$
$$HCl + H_2O \longrightarrow H_3O^+ + Cl^-$$

Acetic acid also reacts with water to form the hydronium ion but in this case the reaction is not more than one or two per cent complete.

$$HAc + H_2O \rightleftharpoons H_3O^+ + Ac^-$$

The difference in acid strength of acetic and hydrochloric or perchloric acids can be demonstrated by comparison of the hydronium ion concentration using a pH meter.

In a basic solvent such as ethylenediamine or butlyamine, both acetic and hydrochloric acids appear to react completely with the solvent.

$$HCl + C_4H_9NH_2 \longrightarrow C_4H_9NH_3^+ + Cl^-$$
$$HAc + C_4H_9NH_2 \longrightarrow C_4H_9NH_3^+ + Ac^-$$

The fact that these acids are of essentially the same strength in strongly basic solvents is demonstrated by titrating them potentiometrically in butylamine. Only a single break is observed whereas if they were of different acid strengths, two breaks would be obtained.

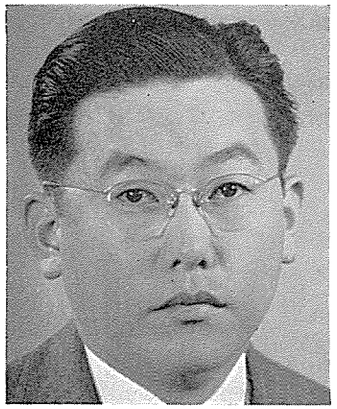
The term "leveling effect" has been applied to this type of phenomena (*8*). In the examples above, butylamine is a "leveling" solvent because it brings hydrochloric and acetic acid to the same level of acidity. Water is a non-leveling solvent for hydrochloric and acetic acids since the inherently greater acid strength of hydrochloric acid is

still exhibited. Water levels perchloric and hydrochloric acids so that they both are of the same strength.

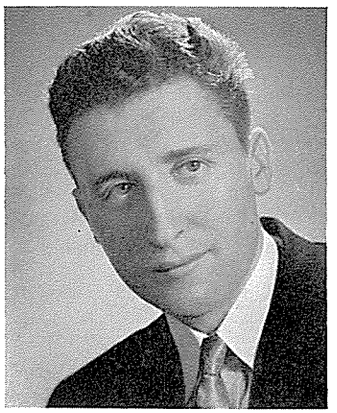
The leveling effect of solvents also applies to bases. In 100 per cent sulfuric acid most bases would react completely with the solvent and thus appear to be all of the same strength. As one goes to less acidic solvents in a series such as,

Sulfuric acid	Water
Acetic acid	Pyridine
Phenol	Butylamine

bases become progressively weaker until all but the strongest lose their basic properties completely. It will thus be seen that a leveling solvent for two bases is one which does not have enough acid strength to react completely with both bases, but does have sufficient acid strength so that at least one of the bases can still behave as a base in comparison with the solvent.



T. Higuchi



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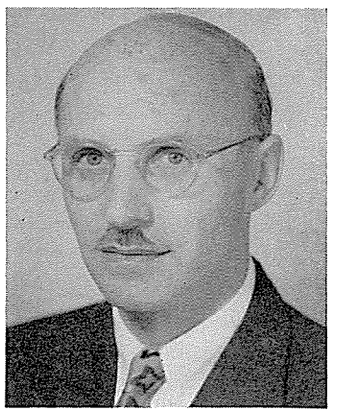


E. G. Wollish

III. TITRATION OF BASES

SOLVENTS AND TITRANTS

When a base is titrated the equilibrium,

$$SH^+ + B \rightleftharpoons BH^+ + S$$

is encountered, where B is the base being titrated, SH^+ is the solvated proton from the titrant and S is the solvent. In order to obtain a sharp end point, this equilibrium must lie far to the right. The most favorable equilibrium will be obtained for any particular base if the solvent has no appreciable basic properties and if the titrant chosen is a very strong acid.

Alcohol dissolves many organic amines which are not soluble in water and has therefore been used for the titration of bases. The basic strength of alcohol is, however, comparatively great (about the same as water) and only aliphatic amines can be titrated successfully.

In a series of classical papers which appeared from 1927 to 1930, Conant, Hall and Werner (*9, 10, 11, 12*) showed that organic amines give excellent end points when titrated in glacial acetic acid with a strong mineral acid. Aromatic amines, which behave as very weak bases in water and alcohol, give sharp breaks at the end point. Much sharper breaks are observed if perchloric acid dissolved in glacial acetic acid is used as the titrant instead of sulfuric or hydrochloric acids in the same solvent. In water there is no difference in the strength of the common strong mineral acids because they all react completely to form the hydronium ion. In acetic acid the mineral acids are found to be of different acid strengths. Kolthoff and Willman (*13*) carried out studies of the conductivity of several acids in acetic acid solution and found the following order of acidity: $HClO_4 > HBr > H_2SO_4 > HCl > HNO_3$. Apparently none of these acids is completely dissociated in glacial acetic acid although perchloric acid is nearly so.

When bases are titrated in glacial acetic acid with perchloric acid, sharper end points result if water is completely excluded. Since the titrant is made up by dissolving 70 to 72 per cent perchloric acid in glacial acetic acid, some water is introduced. This water can be removed by adding the calculated amount of acetic anhydride and allowing the solution to stand for several hours. Although an excess of acetic anhydride does not interfere in some cases, it will react with primary or secondary amines causing erroneous results and often a poor end point. To provide a margin against the presence of excess

acetic anhydride, it is suggested that only about 90 per cent of the theoretical amount of acetic anhydride be added.

Formic acid has been used as a solvent for the titration of bases (*14*). Use of this solvent does not seem to be very practical, however, because it is more unstable than acetic acid and is difficult to obtain anhydrous.

Inert solvents have found some use. Vorlander (*15*) titrated bases in benzene and chloroform using hydrogen chloride in benzene as the titrant. Aniline and other weak bases can be titrated by this method but the escaping tendency of hydrogen chloride from benzene makes this titrant difficult to use and keep. Later modifications involved the use of p-toluenesulfonic acid in benzene (*16*) but the difficulty with this titrant is that it is not a sufficiently strong acid for best results. Other workers (*17, 18, 19*) have found that amines can be titrated very satisfactorily in inert solvents if perchloric acid in glacial acetic acid is used as the titrant. The solvents used include benzene, chlorobenzene, nitrobenzene, chloroform, carbon tetrachloride, ethyl ether, ethyl acetate, petroleum ether and nitromethane. In most of these solvents the end point (methyl violet) is sharper than in acetic acid alone.

Fritz (*20*) found that most aliphatic and heterocyclic amines can be titrated in dioxane with perchloric acid also dissolved in dioxane. Pifer and Wollish (*21*) preferred this titrant to perchloric in acetic acid for titration of salts in acetic acid. They found that some amine salts of strong acids which give almost no break when titrated in acetic acid, can be titrated sharply using the proper proportions of dioxane and acetic acid as the mixed solvent. Some solutions of perchloric acid in dioxane stay clear indefinitely while others quickly become dark brown in color. According to Wollish (*22*), this brown color can be prevented by first shaking the dioxane to be used with a cation exchange resin.

Lavine and Toennies (*23*) found perchloric acid in acetonitrile to be a useful titrant if freshly prepared and standardized. Keen (*24*) used perchloric acid in diethyl Cellosolve for the titration of amines at very low temperatures that would freeze acetic acid or dioxane.

Palit (*25*) introduced a "G-H" solvent consisting of ethylene glycol and some solvent for hydrocarbons such as isopropanol. Usually the glycol and isopropanol were mixed in a 1:1 volume ratio. For titration of bases a standard solution of either hydrochloric or perchloric acid in the same G-H solvent is used as the titrant. Bases as weak as aniline can be titrated by this method but much sharper end points are obtained in acetic acid. Many salts are soluble in this sol-

vent and salts of acids having ionization constants of 10^{-4} or less give sharp end points.

Solutions of perchloric acid in glacial acetic acid, dioxane, etc., are not hazardous in the concentrations used in titrimetric work. Smith (*26*) has found that it is even possible to distill a mixture of 72 per cent perchloric acid and glacial acetic acid without any indication of a violent reaction.

ELECTRODE SYSTEMS

For potentiometric titrations in acetic acid, Conant and Hall (*9*) used a chloranil-calomel electrode system. The indicator electrode consists of a bright platinum wire dipping into the solution being titrated, a small amount of chloranil and tetrachlorohydroquinone being added to set up a redox system sensitive to changes in the acidity of the solution. The reference electrode is a calomel electrode of the older conventional type and is connected to the solution by a salt bridge consisting of a saturated solution of lithium chloride in acetic acid.

In practically all of the more recent work, a glass electrode has been used as the indicator electrode for titrations in acetic acid. Finding that a modern capillary type calomel electrode gives poor equilibrium in acetic acid, Fritz (*19*) suggested the use of a silver wire coated with silver chloride as a reference electrode. This electrode dips directly in the solution being titrated, thus eliminating any cumbersome salt bridge. Using this electrode in conjunction with a glass indicator electrode, successful titrations of bases were made in acetic acid, chlorobenzene, nitrobenzene, acetonitrile, ethyl acetate and chloroform using perchloric acid in acetic acid as the titrant in each case.

Several workers have used a sleeve type calomel electrode as a reference for titrations in acetic acid (*21, 27, 28*). Using either this type or the capillary type calomel in conjunction with the glass electrode, titrations can be carried out in acetonitrile (*29*) and probably in other solvents having a high dielectric constant.

Almost any good direct reading titrimeter may be used for titrations in nonaqueous solvents. The author has performed all of his potentiometric titrations in nonaqueous solvents with either a battery or line operated pH meter using the millivolt scale. This equipment has proved very satisfactory for all titrations except those in solvents having very low dielectric constants. With benzene, toluene, ether and other solvents with low dielectric constants, the very high resistances encountered make electrometric titrations very difficult. LaMer and Downs (*30*), however, showed that titrations such as trichloroacetic acid with diethylamine can be carried out potentiometrically in ben-

zene. Their apparatus consists of a glass crucible with a porous bottom suspended in a small beaker. Platinum electrodes are placed close to both sides of the glass diaphragm. At the start both the beaker and the crucible are filled with a benzene solution of quinhydrone, tetraisoamylammonium iodide (saturated), trichloroacetic acid (0.165 M.) and diethylamine (0.0413 M.). The titration is followed with an ordinary potentiometer using the discharging of a condenser through a ballistic galvanometer (*31*) as a null point indicator.

Very recently, a very simple arrangement has been devised which permits potentiometric titrations to be carried out in dioxane, chloroform and other solvents having very low dielectric constants (*59*). Ordinary glass and calomel electrodes are used but the electrodes are placed very close together. To accomplish this, one electrode is inserted through an opening in the side of the titration vessel while the other electrode is in the usual perpendicular position. This arrangement decreases the resistance of the circuit considerably and permits steady potential readings.

INDICATORS

In 1935, Nadeau and Branchen (*32*) found that crystal violet, α-naphtholbenzein and benzoylauramine are satisfactory indicators for the titration of bases in acetic acid. Methyl violet and crystal violet are now used extensively as indicators in nonaqueous media. One difficulty with these is their lack of a simple color change. As acid is added in excess the color changes from violet to blue, then green and finally to yellow. Most bases can be titrated fairly accurately using methyl violet if the first complete disappearance of a violet tinge is taken as the end point. Seaman and Allen (*28*) have correctly pointed out that for best accuracy each base should first be titrated potentiometrically to determine the indicator shade which marks the true end point. In subsequent titrations of the same base the indicator is neutralized to this color.

Methyl red and modified methyl orange (xylene cyanole) have been recommended as indicators for titrations in dioxane (*20*) and glycol-isopropanol (*25*).

METHODS

Amino Acids

Nadeau and Branchen (*32*) developed a method for titrating amino acids as bases. The sample is dissolved in glacial acetic acid, a measured excess of standard perchloric acid added and the excess acid titrated with a standard base such as guanidine acetate or sodium acetate. In some cases amino acids can be dissolved in glacial acetic

acid and titrated directly with perchloric acid. The back titration procedure, however, facilitates solution of the sample and is generally more satisfactory for amino acids.

PROCEDURE 1

Reagents

0.1 N. Perchloric acid. Mix 8.5 ml. of 72% perchloric acid with 200 or 300 ml. of glacial acetic acid and add 20 ml. of acetic anhydride. Dilute to 1 liter with glacial acetic acid and allow to stand overnight to permit complete reaction of acetic anhydride with the water present.

0.1 N. Sodium acetate. Dissolve 8.2 grams of anhydrous sodium acetate in glacial acetic acid and dilute to 1 liter with acetic acid.

Methyl violet. Dissolve 0.2 grams of methyl violet in 100 ml. of chlorobenzene.

Potassium acid phthalate. Primary standard grade.

Procedure

Dissolve a sample containing two to three milliequivalents of amino acid in exactly 50 ml. of 0.1 N. perchloric acid. Add 2 drops of methyl violet indicator and back-titrate the excess acid with 0.1 N. sodium acetate taking the first permanent violet tinge as the end point.

The perchloric acid is standardized against potassium acid phthalate. About 0.5 grams of potassium acid phthalate is weighed accurately and added to 60 ml. of glacial acetic acid. The mixture is refluxed gently a few minutes to effect solution. After cooling, methyl violet is added and the solution is titrated with perchloric acid to the first disappearance of the violet tinge.

Amines

The most widely applicable method for amines involves titration with standard perchloric acid dissolved in glacial acetic acid. The amine may be dissolved in acetic acid, benzene, chloroform, carbon tetrachloride, chlorobenzene, nitrobenzene, acetonitrile, nitromethane or similar solvents. Benzene and chlorobenzene are particularly recommended since sharper end points are usually obtained in these solvents. Poor end points are obtained if the base is dissolved in acetone or an alcohol.

PROCEDURE 2

The reagents and solutions used are prepared according to the directions given in procedure 1. Dissolve the sample containing two to four milliequivalents in about 50 ml. of chlorobenzene, acetic acid or any of the solvents listed above. Add 2 drops of methyl violet and titrate with 0.1 N perchloric acid to the first disappearance of the violet color. The perchloric acid is standardized against primary standard potassium acid phthalate (see procedure 1).

Highly colored compounds or compounds which fail to give a sharp visual end point should be titrated potentiometrically. A pH meter or other suitable titrimeter is equipped with glass and sleeve type calomel or glass and silver-silver chlo-

ride electrodes (see page 11) and the titration carried out in acetic acid. The potential in millivolts is plotted against the milliliters of titrant used and the inflection point of the curve is taken as the end point.

Although the scope of this method has not been exhaustively studied, it appears to be very broad. Markunas and Riddick (*27*) have titrated over 400 compounds in acetic acid. Most aliphatic and aromatic amines can be titrated unless they are heavily substituted with halogens, nitro, aldehyde or other negative groups. Some typical titration curves are shown in figure 1. Several examples of amines which

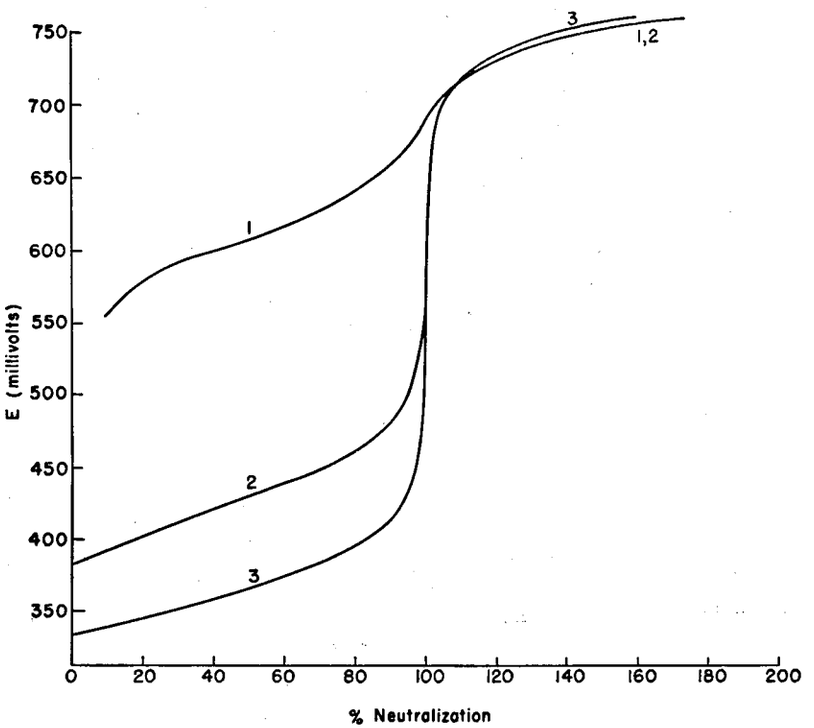


FIGURE 1. Titration in acetonitrile-acetic acid (1:1) with 0.1 N. perchloric acid; glass-calomel electrodes used. Curve 1: p-nitroaniline; curve 2: p-bromoaniline; curve 3: N-methylaniline.

can be titrated are listed in table 1. Also listed are several compounds too weakly basic to be titrated by this procedure.

Smaller amounts of organic bases can be determined using 0.01 N. perchloric acid in acetic acid as the titrant. Typical applications are the determination of basic impurities in refined hydrocarbons (*17*) and hydrocarbon oils (*18*), also the determination of pyridine car-

TABLE 1

Amines Titrated in Acetic Acid	Compounds Which Cannot Be Titrated
Acridine	Acetanilide
Aniline	Benzooxazole
Bromoaniline	Benzothiazole
Brucine	Pyrrole
Butylamine	Hexamethylenetetramine
Nicotinamide	Indole
6-Nitroquinoline	Isatin
Quinoline	Pyrrole
Tribenzylamine	Triphenylamine
2,4,6-Trimethylpyridine	Urea

boxylic acids (*33*). It is even possible to use 0.001 N. perchloric acid for the titration of micro quantities of amines (*34*).

PROCEDURE 3

Reagents

0.001 N. Perchloric acid. Dilute 10 ml. of 0.1 N. perchloric acid in acetic acid to 1 liter with glacial acetic acid.

0.001 N. Potassium acid phthalate. Dissolve 0.2042 grams of potassium acid phthalate (primary standard grade) in hot acetic acid. After cooling to room temperature, the solution is diluted to exactly 100 ml. with glacial acetic acid. Exactly 10 ml. of this solution is diluted with benzene to 100 ml. in a volumetric flask.

Methyl violet. Dissolve 30 mg. of methyl violet in 100 ml. of chlorobenzene.

Procedure

The sample is weighed into a 15 ml. centrifuge tube and dissolved in 1 ml. of benzene. One drop of methyl violet solution is added and the solution is titrated with 0.001 N. perchloric acid to the first permanent blue color. For best accuracy the reagent should be added from a micro burette in "squirts" of 0.002 to 0.005 ml. near the end point. An indicator blank must be run using 1 ml. of benzene and 1 drop of indicator. The perchloric acid is standardized by titrating exactly 1 ml. of standard potassium acid phthalate by this procedure.

Using this procedure as little as 15 to 20 micrograms of aromatic and aliphatic amines can be determined with accuracy of about two per cent. Sharp visual end points are obtained, but only if a minimum of indicator is used. Use of a centrifuge tube as the titration vessel permits observation through a comparatively great depth of solution and thus permits a very low indicator concentration.

While not as widely applicable as titrations in acetic acid, the use of dioxane or ether as a solvent with standard perchloric acid in dioxane as titrant is useful for the titration of nitrogen heterocyclic bases. Hexamethylenetetramine can be titrated by this method but

cannot be titrated in acetic acid, probably because the acetic acid enhances the basic strength of a second nitrogen to the point where it interferes with the titration of the first.

PROCEDURE 4

Reagents

0.1 N. Perchloric acid. Dilute 8.5 ml. of 72% perchloric acid to 1 liter with reagent grade dioxane.

Diphenylguanidine. The technical grade material is purified by recrystallization from toluene, 95% ethanol and again from toluene.

Methyl red. Dissolve 0.1 gram in 100 ml. of methanol.

Procedure

A sample containing 2 to 4 milliequivalents of amine is dissolved in 25 to 50 ml. of either dioxane or ethyl ether. Two drops of methyl red are added and the solution is titrated with 0.1 N. perchloric acid. The perchloric acid is standardized against diphenylguanidine.

Another interesting application is a recent method for the determination of basic impurities in hydrocarbon feed stock. The control of such impurities is an important problem in the petroleum refining industry because these bases tend to poison certain expensive catalysts. In a rapid method developed by Keen (*24*) a sample of C_3-C_4 feed stock is taken with the aid of a "cyclone sampler." This is a cone shaped device which gives entering gas a swirling motion facilitating rapid evaporation and thus quickly cooling the hydrocarbons to a point where they emerge as a liquid (Figure 2). A measured excess of standard perchloric acid in diethyl Cellosolve is added to neutralize the basic impurities in the liquid sample. After evaporation of most of the hydrocarbons, the excess perchloric acid is backtitrated.

PROCEDURE 5

Reagents

Diethyl Cellosolve. The commercial product (Carbide and Carbon) is refluxed over sodium, then distilled.

0.02 N. Perchloric acid. Dilute 1.7 ml. of 72% perchloric acid to 1 liter with diethyl Cellosolve.

0.02 N. Diphenylguanidine. Recrystallize the commercial grade material once from 95% ethanol, twice from toluene and dry at 110° C. Weigh 4.227 grams and make up to exactly 1 liter with diethyl Cellosolve.

Methyl red. A saturated solution in diethyl Cellosolve.

Ethyl ether, anhydrous. Add indicator and neutralize with acid to avoid any blank.

Procedure

Add 5 to 6 ml. of 0.02 N. perchloric acid, accurately measured, to a 250 ml. flask and put a reflux head (*35*) in place. Cool the flask in a dry ice-acetone bath

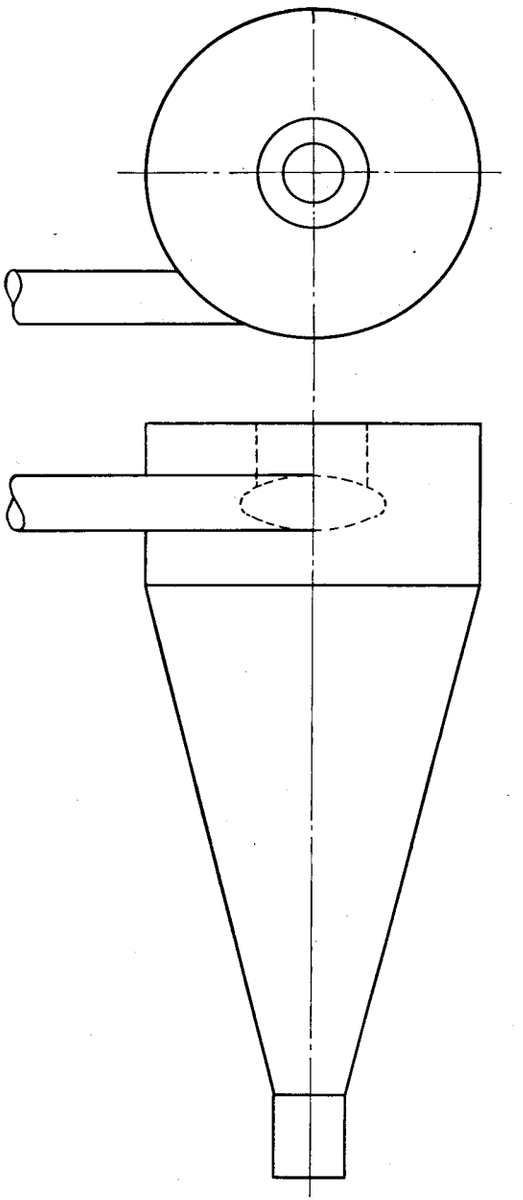


FIGURE 2. Cyclone Sampler.

until boiling of the bath ceases. Wipe the flask and weigh on a platform scale. Allow the cyclone sampler which is connected to the sample line to run for about 0.5 minute then let 80 to 100 grams of liquid run into the flask. Replace the reflux head and quickly reweigh the flask and contents. Let the flask stand for 3 or 4 minutes, then complete evaporation of the hydrocarbons by immersion in a warm water bath. The contents of the flask are rinsed into a 50 ml. beaker with ethyl ether, methyl red is added and the excess perchloric acid is titrated with 0.02 N. diphenylguanidine.

Diethyl Cellosolve was chosen as a solvent for the titrant because acetic acid or dioxane would freeze at the low temperature employed for the neutralization of the amine. A direct titration at —80° C. was partially successful. This was discarded in favor of the above procedure because the end point was sluggish and the results tended to be slightly low.

Salts

Salts of weak carboxylic acids (NaA) react with a strong acid, the weaker acid (HA) being displaced,

$$NaA + H^+ \longrightarrow Na^+ + HA.$$

This salt can be quantitatively titrated if the acid which is liberated is sufficiently weak. In water, the number of salts determinable by this scheme is comparatively few. In acetic acid (*27*) or ethylene glycol-isopropanol (*25*) however, the alkali salts of most carboxylic acids and some inorganic acids can be titrated very accurately with perchloric acid. Indeed potassium acid phthalate, which has long served as a primary standard acid, is now finding use as a primary standard base for perchloric acid solutions in acetic acid. In general the ammonium, lithium, sodium and potassium salts of carboxylic acids give excellent end points. Alkaline earth and magnesium salts give less sharp but satisfactory end points. Salts of other metals give very poor end points and cannot be titrated by this method. Procedure 2, page 13 is recommended for the titration of salts.

Higuchi and Concha (*36*) extended this method to include the titration of amine hydrochlorides as bases. The titration with perchloric acid is carried out slowly, heating to volatalize the hydrogen chloride liberated and thus force the reaction to completion. An ingenious modification introduced by Pifer and Wollish (*21, 37*) employs the use of mercuric acetate in the potentiometric titration of amine halide salts in acetic acid. The halide is tied up as undissociated HgX_2 and the acetate ion liberated can be titrated as a base with perchloric acid. Mercuric acetate is essentially undissociated in acetic acid (*13*) and the excess therefore does not interfere.

$$2RNH_3^+X^- + HgAc_2 \text{ (excess)} \longrightarrow 2RNH_3^+Ac^- + HgX_2$$
$$RNH_3^+Ac^- + HClO_4 \longrightarrow RNH_3^+ClO_4^- + HAc$$

Although methyl violet can be used as a visual indicator in some cases, Pifer and Wollish recommend potentiometric determination of the end point. The sample is dissolved in acetic acid but perchloric acid in dioxane is used as the titrant because its use gives a sharper end point.

PROCEDURE 6

Apparatus

Beckman pH meter (model G) or similar titrimeter.

Beckman glass electrode (No. 1190-90).

Beckman calomel electrode (No. 1170).

Reagents

0.1 N. Perchloric acid. Dissolve 8.5 ml. of 72% perchloric acid in 1 liter of dioxane.

Mercuric acetate. Dissolve 6 grams of mercuric acetate in 100 ml. of hot glacial acetic acid and cool to room temperature.

Procedure

The sample weight is chosen so that about 30 ml. of 0.1 N. perchloric acid will be required for the titration. Weigh the sample into a 250 ml. beaker and dissolve in 80 ml. of glacial acetic acid, heating to effect solution if necessary. If the sample is the hydrohalide salt of an organic base, add 10 ml. of mercuric acetate solution. Titrate with 0.1 N. perchloric acid using the millivolt scale of the pH meter. The end point is taken as the point where $\Delta E/\Delta V$ is a maximum.

It is possible to titrate amine sulfates and nitrates by this procedure without the addition of mercuric acetate. For sulfates the end point is reached when the sulfate has been neutralized to the bisulfate,

$$(RNH_3)^+{}_2SO_4^= + H^+ClO_4^- \longrightarrow 2RNH_3^+ + HSO_4^-.$$

Table 2, taken from the work of Pifer and Wollish (*21, 37*), lists several salts which have been titrated.

A surprising number of strictly inorganic salts can be dissolved in acetic acid and titrated as bases. Pifer and Wollish (*38*) have re-

TABLE 2

Salts Determined by Pifer and Wollish Method

Choline chloride	Pyridoxine hydrochloride
Choline dihydrogen citrate	Tetraethylammonium bromide
Codeine phosphate	Thiamine hydrochloride
Histidine monohydrochloride	Thiamine nitrate

ported the successful potentiometric titration of the following anions (taken as the sodium salts):

Acetate	Iodate
Azide	Iodide
Bicarbonate	Molybdate
Bisulfite	Nitrate
Bromate	Nitrite
Bromide	Peroxide
Carbonate	Phosphate
Chlorate	Silicate
Chloride	Sulfate
Cyanide	Sulfide
Fluoride	Sulfite
Hydroxide	Thiocyanate
Hypophosphite	Tungstate

These titrations were carried out potentiometrically according to procedure 6. To get many of these salts in solution it is necessary to put the sample through a 100 to 200 mesh sieve and then reflux gently with acetic acid. In a few cases the sample is first dissolved in 5 ml. of water, then about 80 ml. of acetic acid is added and the titration carried out potentiometrically.

Mixtures

Titration in nonaqueous media offers the most convenient method for differentiating quantitatively between primary, secondary and tertiary amines in mixtures. Tertiary amines are determined by first treating the mixture with acetic anhydride in acetic acid. This converts primary and secondary amines into almost neutral acetylation products. Tertiary amines are not affected and can be titrated with perchloric acid. The excess acetic anhydride does not interfere with titration of tertiary amines and therefore does not have to be removed. The following procedure is taken from the work of Wagner, Brown and Peters (*39*).

PROCEDURE 7

Apparatus

A potentiometric titrimeter such as the Beckman model M or Precision-Shell. The titrimeter is equipped with glass and calomel electrodes.

Reagents

0.1 N. Perchloric acid. Mix 8.5 ml. of 72% perchloric acid with 1 liter of glacial acetic acid.

Procedure

An acetylating mixture consisting of 20 ml. of acetic anhydride and 2 ml. of acetic acid is added to a sample which should not weigh more than 2 grams or contain more than 1 gram of water. The mixture is allowed to stand three hours at room temperature. If sterically-hindered secondary amines are present, refluxing for one hour is required. Thirty milliliters of acetic acid is added and the solution is titrated potentiometrically with 0.1 N. perchloric acid.

Primary amines react with salicylaldehyde to form Schiff bases which are weaker than the primary amine. This permits the determination of primary amines in the presence of secondary and tertiary bases. By titrating aliquots of an amine mixture, then doing a second titration after reaction with salicylaldehyde, the primary amine content of the mixture can be determined by difference. Wagner, Brown and Peters (*40*) used benzene-isopropanol as the solvent and carried out the titration of aliphatic amine mixtures electrometrically. Siggia, Hanna and Kervenski (*41*) used ethylene glycol-isopropanol as a solvent for the potentiometric titration of aromatic amine mixtures by a similar scheme. Their procedure is given below.

PROCEDURE 8

Reagents

Ethylene glycol-isopropanol. A 1:1 mixture is used.

1 N. Hydrochloric acid. 96 ml. of concentrated hydrochloric acid is diluted to 1 liter with ethylene glycol-isopropanol.

Salicylaldehyde. From bisulfite addition compound.

Procedure

A. Total amines. A sample containing approximately 0.02 mole of total amines is weighed into a 150 ml. beaker and dissolved in 50 ml. of ethylene glycol-isopropanol. The sample is titrated potentiometrically with 1 N. hydrochloric acid in ethylene glycol-isopropanol using an ordinary pH meter. The neutralization point is obtained from a plot of apparent pH against milliliters of acid.

B. Secondary plus tertiary amines. A sample containing about 0.02 mole of secondary plus tertiary amine is dissolved in 50 ml. of ethylene glycol-isopropanol and 5 ml. of salicylaldehyde is added. The mixture is stirred thoroughly then allowed to stand for 0.5 hour at room temperature. It is then titrated potentiometrically with 1 N. hydrochloric acid in glycol-alcohol. The difference in milliequivalents of amine obtained in A and B represents the amount of primary amine present in the sample.

By three titrations under different conditions a mixture of primary, secondary and tertiary amines can be completely analyzed.

meq. $(1^\circ + 2^\circ + 3^\circ)$	$= a$	(procedure 2 or 8A)
meq. 3°	$= b$	(procedure 7)
meq. $2^\circ + 3^\circ$	$= c$	(procedure 8B)
meq. 2°	$= c - b$	(by calculation)
meq. 1°	$= a - c$	(by calculation)

INTERFERENCES

Water and alcohol interfere with titrations of weak bases carried out in acetic acid, dioxane and many other solvents. This interference is probably due to the weak basic properties of water and alcohol. In acetic acid, water in amounts up to 1.5 to 3 per cent of the original solvent has little effect on the accuracy. Greater amounts cause high results and very poor end points. Although no quantitative data are available, it appears that slightly larger amounts of alcohol can be tolerated. Aqueous or alcoholic solutions of tertiary amines or alkali salts of carboxylic acids can be titrated by first treating with acetic anhydride to react with the water or alcohol.

Most inorganic ions interfere. The cations (except for those of the alkali and alkaline earth metals and a few others) react with acetic acid forming slightly dissociated acetates and liberating hydrogen ions.

$$M^{++} + 2HAc \longrightarrow MAc_2 + 2H^+$$

Except for perchlorate, anions are more or less titrated as bases.

Very weak organic bases constitute another important interference. This occurs when the interfering substance is a slightly weaker base than the compound being titrated but still too weak to give a sharp end point itself. This situation is often encountered in the titration of compounds like hexamethylenetetramine, which have nitrogen atoms of gradually decreasing basicity.

PRECISION AND ACCURACY

The accuracy and precision of titrations carried out in either aqueous or nonaqueous solvents depends chiefly on the sharpness of the end point and the precision with which the buret can be read. The coefficient of cubic expansion of most organic solvents is much greater than that of water but error can usually be prevented by avoiding temperature changes during the titration. Most aliphatic amines, aromatic amines and alkali metal salts of carboxylic acids may be titrated in glacial acetic acid with an accuracy and precision of ± 0.2 per cent. Weaker bases such as nitroaniline and caffeine give less sharp end points and the attainable precision is correspondingly less. Table 3 lists the accuracy which can usually be expected when compounds are titrated according to various procedures.

TABLE 3

Estimated Precision and Accuracy

Procedure	Precision and Accuracy
1	± 0.3%
2	± 0.2%
3	± 0.2%
4	± 0.3%
5	± 1.0%
6	± 0.2%
7	± 0.3%
8	± 0.6%

IV. TITRATION OF ACIDS

SOLVENTS AND TITRANTS

The ideal solvent for titration of acids should dissolve readily a large variety of acids and should have no acidic properties itself. The titrant should be a strong base dissolved in a non-acidic solvent and should be stable on standing.

Alcohols have been widely used as solvents for the titration of organic acids. Alcoholic potassium hydroxide or sodium alkoxide in the corresponding alcohol is generally employed as the titrant. The acidic properties of alcohol are, however, sufficiently great to limit use to titration of carboxylic acids and other acids with a pK (in water) not greater than about 6. If acids are dissolved in benzene or toluene and titrated with sodium ethoxide in ethanol, the sharpness of the end point is improved (*7*). Ruehle (*42*) dissolved asphalt and pitches in dioxane-butanol, acetone-butanol or anisol-butanol and titrated the acidic constituents potentiometrically with sodium butoxide.

Sodium methoxide in benzene-methanol is an excellent titrant (*43*). A 0.1 to 0.2 N. solution contains about one volume of methanol to 6 volumes of benzene, this being the minimum amount of methanol required to obtain a homogeneous solution. This titrant generally gives sharper end points than does sodium alkoxide in alcohol alone because less alcohol is introduced into the solution by the titrant itself. It has just recently been found that a 0.1 N. solution of potassium methoxide requires only 1 volume of methanol to about 12 volumes of benzene (*29*). The latter titrant has not yet been fully evaluated but it appears to be superior to sodium methoxide for the titration of the more weakly acidic phenols, enols and imides.

An outstanding development has been the introduction of anhydrous ethylenediamine as a solvent for the titration of phenols and other very weak acids (*44*). Sodium aminoethoxide in ethylenediamine-ethanolamine and sodium methoxide in benzene-methanol have been used as titrants in conjunction with this solvent. Ethylenediamine is valuable not only because it increases the effective strength of weak acids, but also because it is an excellent solvent for all types of acidic substances. For the titration of most phenols the ethylenediamine used should be essentially free from water and other "acid" impurities. Moss *et al* (*44*) recommend the removal of even the last one per cent of water from ethylenediamine. For titration of slightly stronger acids, a purity of 95 to 100 per cent is satisfactory. Ethylenediamine of this purity is now commercially available. Unfortunately

ethylenediamine of greater than 76 per cent purity is relatively expensive due to the formation of a stable hydrate which is not decomposed by distillation. The anhydrous material is usually prepared by treatment of 70 to 76 per cent ethylenediamine with sodium hydroxide and sodium metal, then distilling (*45*). Purification of either 70 or 95 per cent ethylenediamine by azeotropic distillation with benzene has also been recommended (*46*).

Butylamine can also be used as a solvent for the titration of weak acids. It is not as good a solvent as ethylenediamine but will dissolve many acids and is somewhat cheaper. Butylamine is readily available and the commercial product requires no purification.

Dimethylformamide (DMF) is an excellent solvent for a wide variety of compounds. It is commercially available at a reasonable price and requires no further purification. DMF is essentially odorless. Using sodium methoxide in benzene-methanol as titrant, DMF is recommended for the titration of all except very weak organic acids. These require a more basic solvent such as ethylenediamine or butylamine.

Much stronger bases than sodium alkoxides have been proposed as titrants. Sodium triphenylmethane is an extremely powerful base. It has the advantage of being soluble in ether or aromatic hydrocarbons. Because of its deep blood red color, sodium triphenylmethane serves as its own indicator in much the same manner as permanganate does in redox titrations. Unfortunately it is so readily destroyed by oxygen or moisture that it is very difficult to use quantitatively.

Lithium aluminum hydride in tetrahydrofurane has been used by Higuchi, Lintner and Schleif (*47*) for the quantitative determination of alcohols and phenols. This is actually a redox reaction but is closely related to an acid base reaction.

$$4ROH + LiAlH_4 \longrightarrow ROLi + (RO)_3Al + 4H_2.$$

By reacting lithium aluminum hydride with a secondary amide, lithium aluminum amides can be prepared which are soluble in tetrahydrofurane and can be used for the titration of alcohols and phenols by a true acid-base reaction (*48*),

$$4ROH + (R_2N)_4LiAl \longrightarrow ROLi + (RO)_3Al + 4R_2NH.$$

Lithium aluminum amides are said to be rather insensitive to oxygen, an advantage over lithium aluminum hydride which reacts readily with oxygen of the atmosphere. Although a thorough study has not been made, it appears that both lithium aluminum hydride and lithium aluminum amides enter into side reactions with carbonyl and

other groups. Another difficulty is that tetrahydrofurane must be purified every few days because of peroxide formation.

ELECTRODE SYSTEMS

Conventional glass-calomel electrode systems can be used for titrations in alcohol solution. Titration in basic solvents presents a more difficult problem because of the inability of the glass electrode to function as an indicator electrode in such solutions. In ethylenediamine, hydrogen-antimony, hydrogen-calomel and antimony-antimony electrode systems have been used (*44*). Of these the latter is the most convenient and ingenious. The indicator electrode is an antimony rod dipping into the solution being titrated. It is prepared by sucking the molten metal into a $^{1}\%_{0}$ standard taper thermometer joint and chipping off the glass below the joint after cooling. The reference electrode is similarly prepared and is mounted in the buret below the stopcock. This system is a modification of that suggested by Willard and Boldyreff (*49*). The buret tip is immersed in the solution being titrated, thus making contact between the two electrodes. This arrangement permits continual flushing of the reference electrode to avoid diffusion (figure 3).

Electrometric titrations in butylamine have been carried out using an antimony-glass electrode system (*43*). Here the glass electrode appears to function as the reference while the antimony is the indicator electrode. One advantage of this system is that no salt bridge is required.

Antimony and calomel electrodes may be used for titrations in dimethylformamide (*29*). This system gives steady potentials and a rather large potential break at the end point. In some cases this break is more gradual than would be expected from the very sharp end points obtained with visual indicators.

In tetrahydrofurane, Higuchi *et al* used a platinum-calomel combination for titrations with lithium aluminum hydride. A sharp break is obtained at the end point due to the strong reducing power of lithium aluminum hydride.

INDICATORS

Phenolphthalein and thymolphthalein have been used for titrations in benzene, chloroform, alcohols and other solvents. Much more satisfactory, however, are thymol blue and azo-violet (p-nitrobenzeneazoresorcinol). Thymol blue gives an excellent end point (yellow to blue) for titrations carried out in benzene, butylamine, dimethylformamide, pyridine and similar solvents. It is unsatisfactory in ethylenediamine. Azo violet is a weaker indicator acid than thymol blue and is used for

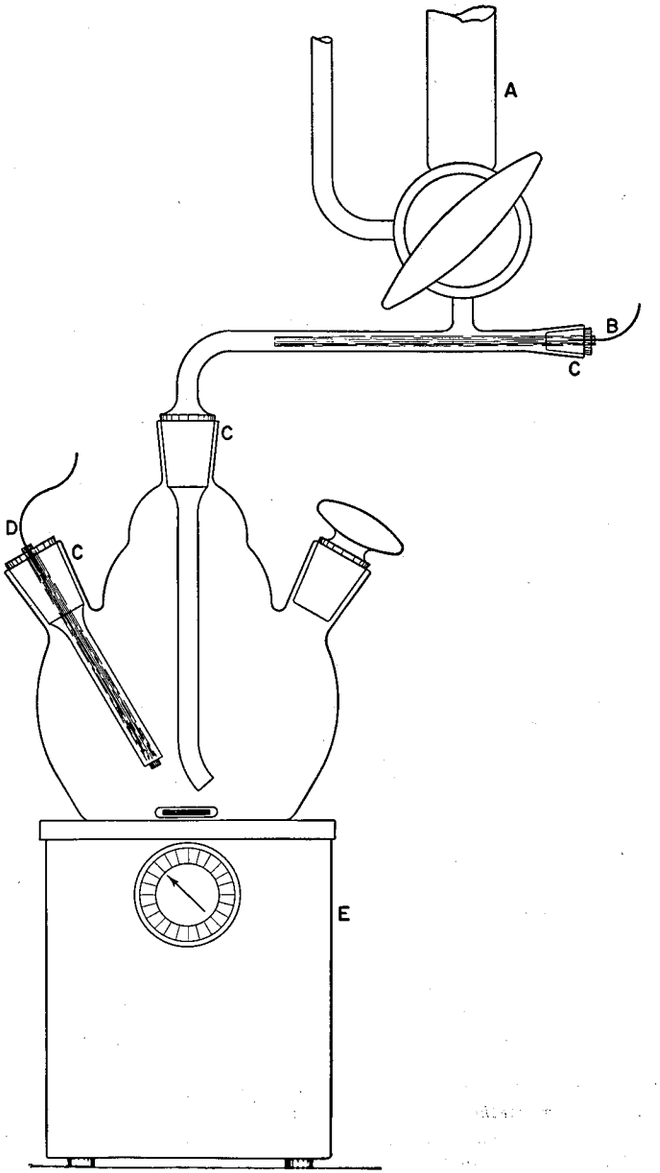


FIGURE 3. Titration assembly. A, 50 ml. buret; B, antimony reference electrode; C, $^{10}\%_{0}$ T joints; D, antimony indicator electrode; E, magnetic stirrer.

the titration of acids too weak to give sharp thymol blue end points. Azo violet gives very sharp end points (red to blue) in ethylenediamine, butylamine, pyridine and dimethylformamide. No satisfactory color change is observed in benzene and other inert solvents.

o-Nitroaniline is a still weaker indicator acid and is used as an indicator for the titration of phenol and other acids too weak to be titrated using either thymol blue or azo violet. This indicator gives a fairly sharp change (yellow to orange red) in dimethylformamide or ethylenediamine but does not appear to function as an indicator in butylamine, benzene or alcohol.

Qualitative observations have revealed that many other nitro compounds act as indicators in basic solvents (*29*). Some of these are slowly or incompletely reversible but others apparently have excellent indicator characteristics.

METHODS

Carboxylic Acids

Most carboxylic acids are sufficiently strong so that analysis is a comparatively simple matter. Titration in alcohol with an aqueous solution of sodium hydroxide using phenolphthalein indicator is a familiar procedure. Using this method, however, fatty acids form objectionable soaps and polyfunctional acids often give poorly defined end points. The following procedure is recommended because it avoids these difficulties and gives sharper end points.

PROCEDURE 9

Apparatus

Buret, 10 ml. capacity which can easily be read accurate to 0.01 ml.

Titration vessel. A 50 ml. covered beaker or flask. (See figure 4).

Magnetic stirrer. Small pieces of nails or heavy wire sealed in glass tubing make convenient stirring bars.

Reagents

Azo violet. Saturated solution of p-nitrobenzeneazoresorcinol in benzene.

Benzene. A.C.S. grade.

Benzene-methanol. Mix 4 volumes of benzene with 1 volume of methanol.

Dimethylformamide. Technical grade (du Pont).

0.1 N. Sodium methoxide. About 5 grams of freshly cut sodium metal is washed in methanol, then dissolved in 100 ml. of absolute methanol. The reaction of sodium with the methanol can be controlled by occasional immersion of the reaction vessel in ice water. When the reaction is complete 150 ml. of methanol and 1500 ml. of benzene is added and the reagent is stored in a pyrex container protected from carbon dioxide and moisture.

Thymol blue. Dissolve 0.3 gram of thymol blue in 100 ml. of methanol.

Procedure

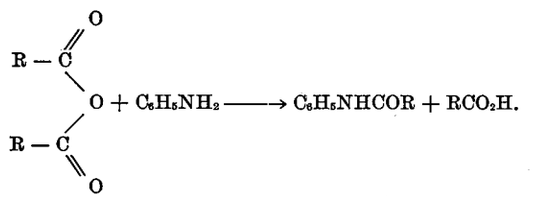
A sample containing 0.3 to 0.8 milliequivalents of acid is dissolved in 20 ml. of either benzene-methanol or dimethylformamide. Two drops of thymol blue indicator are added and the solution is titrated with sodium methoxide to a clear blue color. If dimethylformamide is used as the solvent, the acid impurities should be neutralized before the sample is added. The sodium methoxide is standardized against benzoic acid.

Some dibasic acids are too weak to give a sharp thymol blue end point. Such compounds can be titrated using dimethylformamide solvent and azo violet indicator.

Best results are obtained if titrations in dimethylformamide are carried out in vessels designed to prevent absorption of carbon dioxide from the atmosphere during the titration. A beaker covered with a cardboard with a hole to admit the buret tip may be used (figure 4). Use of a magnetic stirrer in conjunction with this titration assembly adds greatly to the convenience of the method.

Using benzene-methanol as the solvent, the above procedure is applicable to the direct titration of acid chlorides and anhydrides (*43*), both behaving as monobasic acids in the absence of water.

Siggia and Hanna (*50*) have devised a method for the determination of carboxylic anhydrides in the presence of their acids. A weighed excess of aniline is added to the sample being analyzed. The acid anhydride present reacts quantitatively with the aniline,



Ethylene glycol-isopropanol is then added and the excess aniline is titrated potentiometrically with hydrochloric acid in glycol-isopropanol.

ENOLS AND IMIDES

Most enols and imides can be titrated in dimethylformamide using thymol blue or azo violet indicator (*51*). Theobromine and a few other compounds which are difficultly soluble in DMF can be titrated in ethylenediamine using azo violet indicator. Very weakly acidic enols and imides can usually be titrated in ethylenediamine using o-nitroaniline indicator.

PROCEDURE 10

Apparatus

The apparatus required is the same as described in procedure 9, page 28.

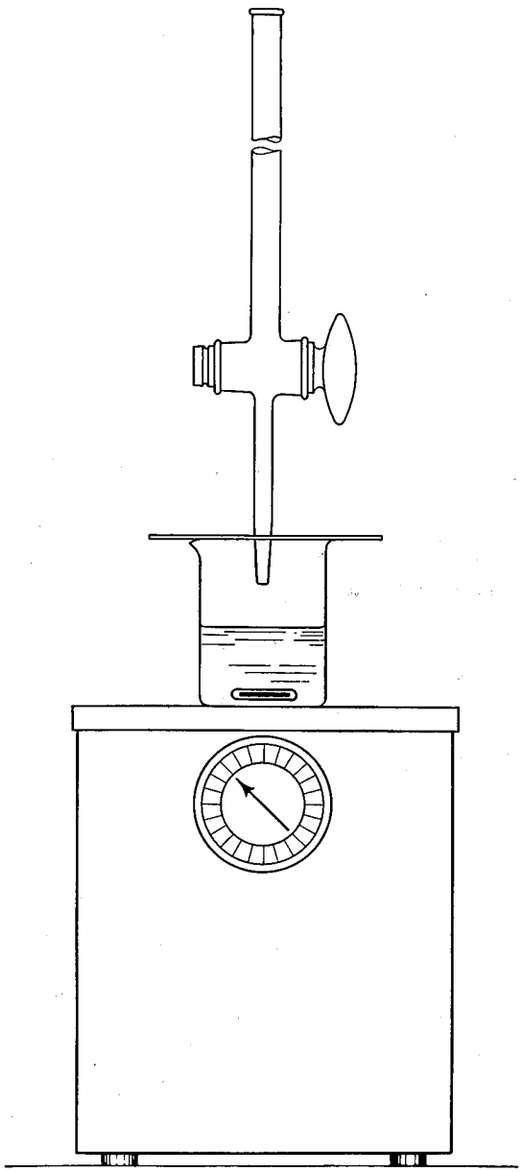


FIGURE 4. Titration assembly.

Reagents

Ethylenediamine. 95 to 100% as purchased commercially.

o-Nitroaniline. Dissolve 0.15 g. of o-nitroaniline in 100 ml. of benzene.

0.1 N. Potassium methoxide. Place 20 ml. of methanol and 50 ml. of dry benzene in a large flask or pyrex bottle. Add about 4 grams of freshly cut potassium metal and cover the flask or bottle loosely. If necessary the speed of the reaction can be controlled by immersion in cold water. When the reaction is complete, add 55 ml. of methanol and mix thoroughly. Dilute to 1 liter with dry benzene, adding the first 500 ml. rather slowly with stirring. If cloudiness persists at any point during the dilution with benzene, add enough methanol to clear the solution before continuing. Store in a pyrex container protected from carbon dioxide and moisture.

Preparation of the other reagents required is described in procedure 9, page 28.

Procedure

A. Add two drops of azo violet to 15 to 20 ml. of dimethylformamide and neutralize the acid impurities with 0.1 N. sodium or potassium methoxide. Add the sample (containing 0.3 to 0.8 milliequivalents of enol or imide) and titrate to the first clear blue color.

B. Add two drops of o-nitroaniline to 15 to 20 ml. of ethylenediamine and neutralize the acid impurities. Add the sample (0.1 to 0.4 milliequivalents) and titrate with sodium or potassium methoxide taking as the end point the first conversion of the indicator from yellow to orange or orange red.

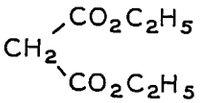
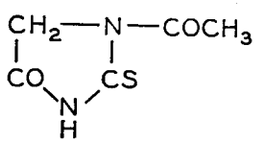
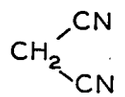
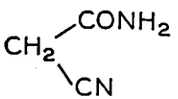
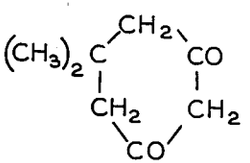
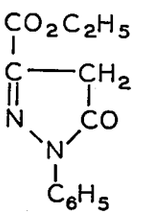
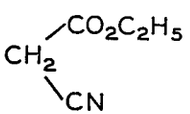
Enols of the type A—CH_2—A′ are sufficiently acid to permit titration according to this procedure provided A and A′ are groups possessing suitable electron withdrawing properties. If A and A′ are any combination of —$\overset{\overset{O}{\|}}{C}$—R, —$\overset{\overset{O}{\|}}{C}$—H, —$\overset{\overset{O}{\|}}{C}$—OR, —$\overset{\overset{O}{\|}}{C}$—NHAr or —C≡N, accurate titration in dimethylformamide is possible. The amide group, —$\overset{\overset{O}{\|}}{C}$—$NH_2$, has weaker electron withdrawing properties. This is shown by the fact that while malononitrile gives a good azo violet end point, cyanoacetamide gives a very poor end point and malonamide is not at all acid toward azo violet. Cyanoacetamide does give a satisfactory end point in ethylenediamine using o-nitroaniline indicator (procedure 10B); malonamide is slightly acid to this indicator.

The carboxyl groups in cyanoacetic acid and malonic acid can be titrated but these compounds apparently have no further acidic properties, indicating that the —$\overset{\overset{O}{\|}}{C}$—ONa group has very slight if any electron withdrawing properties. Compounds of the type A—CH_2—CH_2—A′ are not acid toward azo violet even if A and A′ are strong

electron attracting groups. Examples of enols which have been titrated by the above procedure are listed in table 4.

TABLE 4

Enols Titrated By Procedure 10

$C_6H_5NHCOCH_2COCH_3$	
	
	
$C_6H_5COCH_2COC_6H_5$	
	
$CH_3COCH_2COCH_3$	

Compounds having the configuration A—NH—A′ can be titrated accurately as acids if A and A′ are any combination of the following groups: —C(=O)—R, —C(=O)—H, —C(=O)—OR, —C(=O)—NHAr. If either A or A′ is the —C(=O)—NH_2 or —C(=O)—NHR group the success of the titration is uncertain. For example acetylurea gives a very poor end point yet hydrantoin, which is essentially the cyclic equivalent of acetylurea gives an excellent azo violet end point. Although the electron attracting properties of aryl groups are somewhat less than the above listed groups, a phenyl group in the proper position will noticeably increase

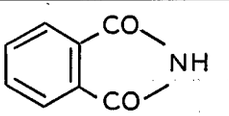
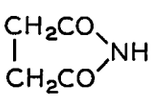
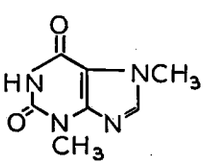
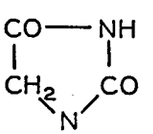
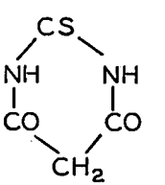
the acidity of an imide. This is illustrated by the fact that acetylacetanilide ($CH_3COCH_2CONHPh$) gives a much sharper end point than acetylurea ($CH_3CONHCONH_2$) and that oxanilide (PhNHCOCONHPh) can be titrated as a monobasic acid while oxamide ($NH_2COCONH_2$) does not even react acidic to azo violet.

Imides containing a thiocarbonyl group are considerably stronger acids than the analogous compounds containing a carbonyl group. Thus s-diphenylthiourea can be titrated according to procedure 10A and phenylthiourea using procedure 10B, but neither s-diphenylurea or phenylurea can be determined by either procedure. Even thiourea is weakly acidic toward o-nitroaniline in ethylenediamine although no definite end point is obtainable.

Table 5 lists specific compounds which have been titrated by the above procedures.

TABLE 5

Imides Titrated By Procedure 10

$C_6H_5NHCSNHC_6H_5$	
$NH_2CSNHCSNH_2$	
$NH_2CSCSNH_2$	
	
$C_6H_5NHCSNHC_6H_{12}$	

Using thymol blue as indicator and dimethylformamide as the solvent, barbiturates can be titrated as monobasic acids (*52*). Since common tablet excipients such as starch, powdered sugar and magnesium stearate are not acidic, the direct titration of barbiturates in powdered

tablet samples is possible. It is also possible to isolate the barbiturates by extraction and evaporation of the extracting solvent, then dissolve the residue in dimethylformamide and titrate with sodium methoxide.

SULFONAMIDES

The most widely used methods for macro quantities of sulfa drugs involve titration of the primary amino group with standard sodium nitrite. The end point is either determined potentiometrically or with starch-iodide paper as an external indicator. Because of the acidity of the —SO_2NH— group, titration of sulfa drugs as acids in nonaqueous solvents is possible. This method is more convenient and accurate than the diazo procedure. Although other acids interfere, the alkalimetric method is also valuable in that it offers a different method of attack. Sulfathalidine and sulfasuxidine, which cannot be analyzed by the diazo method because they lack a primary amino group, can be titrated as acids. Of the common sulfa drugs, only sulfaguanidine cannot be determined by the alkalimetric method. This is useful in some cases because sulfaguanidine does not interfere with the determination of other sulfonamides by this method.

Procedure 9 is recommended for the determination of sulfa drugs using dimethylformamide solvent and thymol blue indicator. Pure samples of sulfathiazole, sulfadiazine, sulfapyridine, sulfamerazine, sulfasuxidine and sulfathalidine were titrated with an accuracy of $\pm$ 0.2% by this method (*53*). Sulfanilamide is not acid to thymol blue but can be titrated accurately in butylamine using azo violet indicator. A mixture such as sulfathiazole-sulfanilamide can be analyzed by titrating the sulfathiazole in dimethylformamide with thymol blue, then titrating both sulfa drugs in a second sample using butylamine solvent and azo violet indicator.

Apparently there is considerable difference in the acidity of the aryl sulfonamides of primary aromatic and primary aliphatic amines. Compounds of the type $ArSO_2NHAr$ give very sharp end points in dimethylformamide while those of the type $ArSO_2NHR$ require a more basic solvent such as butylamine and give only mediocre end points.

PHENOLS

Titration of phenols as acids has long been an inviting prospect but the very weakly acidic nature of phenols has made this difficult. Use of ethylenediamine as a solvent, suggested in 1948 by Moss, Elliott and Hall (*44*), permits a satisfactory alkalimetric determination of phenols.

PROCEDURE 11

Apparatus

Buret and electrode assembly, similar to that shown in figure 3, page 27.

Titrimeter. A Beckman model G pH meter or other direct reading potentiometric titrimeter.

Reagents

Ethylenediamine, anhydrous. Commercial 70% grade is purified by the method of Putnam and Kobe (*45*) by refluxing with sodium hydroxide and distilling over sodium. If the 95 to 100% material (also commercially available) is used as the starting product, the last traces of water may be removed by distilling over sodium.

0.1 N. Sodium aminoethoxide. Dissolve approximately 2.5 g. of sodium, which has been washed in ethanol and ethanolamine, in 100 ml. of ethanolamine with cooling. Dilute to 500 ml. with ethylenediamine.

Ethanolamine. Purify the commercial product by distilling three times through a 2-foot Vigreux column (*54*).

Procedure

A sample of 0.1 to 1 g. is weighed into the titration flask and dissolved in 75 ml. of ethylenediamine. The buret tip and reference electrode are flushed with titrant and the flask connected to the buret. The phenol is then titrated potentiometrically with 0.1 N. sodium aminoethoxide taking the inflection of the curve as the equivalence point. The titrant is standardized against pure benzoic acid using the same procedure. A blank should be run since ethylenediamine is likely to contain some acid impurities.

This method appears to be widely applicable. Dark colored resins can be titrated and separate breaks are obtained for the carboxylic acid and phenolic constituents. Monohydric phenols give good end points but resorcinol gives two gradual breaks. Even boric acid gives three slight but distinct breaks.

The purity of the ethylenediamine used seems to be an important factor in determining the success of this method. Moss *et al* found that with 99 to 100 per cent ethylenediamine, phenol gives a sharp end point break of 180 to 200 millivolts. In 80 per cent ethylenediamine, however, the break only amounts to about 20 millivolts. Removal of even the last one per cent moisture is recommended.

Katz and Glenn (*46*) used this method to determine phenols in coal hydrogenation products. A recorder was used to effect more convenient and accurate location of the end point. Small, equal increments of titrant are added near the end point and the recorder is set back to zero after the addition of each increment. The volume of titrant corresponding to the largest potential jump is the correct end point.

Recent work has indicated that phenols can be successfully titrated as acids using visual indicators (*55*). Potassium methoxide in benzene-methanol is the recommended titrant and either dimethylformamide

or ethylenediamine is used as the solvent, depending on the type of phenol being titrated. This method is no more accurate than that of Moss *et al* but does have the advantage of being faster and requiring less elaborate apparatus.

Phenol, naphthol and their alkyl derivatives are titrated according to procedure 10B, page 31. The o-nitroaniline end point is not as sharp as might be desired but accuracy of ± 0.5 to 0.6 per cent or better is obtainable without difficulty. Phenols which have an aldehyde, keto, ester or nitro group in the ortho or para position are stronger acids than unsubstituted phenols. These may be titrated accurately in dimethylformamide using azo violet indicator (procedure 10A). The carboxyl group does not enhance the acidity of a phenol. One halogen increases the acidity slightly but procedure 10B must still be used. Two or more halogens (such as in 2,4-dibromo-1-naphthol) increase the acidity so that a sharp azo violet end point is obtained. Resorcinol cannot be titrated with indicators in either dimethylformamide or ethylenediamine presumably because of the weak acidic nature of the second phenolic group. Examples of phenols which have been titrated are listed in table 6.

TABLE 6

Titration of Phenols

Procedure 10A	Procedure 10B
2-Aceto-1-naphthol	p-tert.-Amylphenol
o-Hydroxyacetophenone	p-Benzylphenol
p-Hydroxybenzaldehyde	p-Bromophenol
p-Hydroxypropiophenone	o-Hydroxydiphenyl
8-Hydroxyquinoline	2,2'-Methylenebis(4-methyl-6-tert. butylphenol)
Methyl salicylate	2-Naphthol
Resacetophenone	Phenol
Trichlorophenol	Phloroglucinol · $2H_2O$
Vanillalacetone	
Vanillin	

SALTS

Salts are formed by the reaction of an acid and a base. If the basic constituent of a salt is not too strong, that salt can be titrated with a strong base such as sodium hydroxide or sodium methoxide.

$$BH^+ + OH^- \longrightarrow B + HOH$$
$$BH^+ + OCH_3^- \longrightarrow B + CH_3OH$$

In water or alcohol, the scope of such titrations is limited chiefly to the mineral acid salts of aromatic amines. In basic nonaqueous solvents, however, the salts of stronger bases such as ammonia and aliphatic amines can also be titrated with very good results (*56*).

PROCEDURE 12

Reagents

Reagents and solutions used are described in procedure 9, page 28, and in procedure 10, page 29.

Procedure

With sodium methoxide, neutralize the acid impurities in 20 ml. of dimethylformamide using thymol blue or in 20 ml. of ethylenediamine using azo violet indicator. Add the sample (containing about 0.3 to 0.8 milliequivalents) to the neutralized solvent and titrate with 0.1 N. sodium methoxide to a clear blue color. A solid sample, difficultly soluble in dimethylformamide or ethylenediamine may be dissolved in 1 ml. of water, neutralized ethylenediamine added and the salt titrated. If the sample is an aqueous solution, a 1 ml. portion is mixed with 20 ml. of ethylenediamine and titrated as before.

Salts of the type B · HA can be titrated by this procedure if:

1. the salt is soluble in a suitable organic solvent,
2. the acid constituent, HA, is sufficiently strong,
3. the basic constituent, B, is not too strong.

Ethylenediamine and dimethylformamide are the most satisfactory solvents for the titration of salts. Ethylenediamine is an excellent solvent for most salts, although many sulfates, phosphates, oxalates and carbonates do not dissolve. Sharp end points can be obtained using azo violet indicator. Aqueous salt solutions can be analyzed by adding a large excess of ethylenediamine to the sample before carrying out the titration. Solid samples, such as ammonium sulfate, which do not dissolve readily in ethylenediamine may be dissolved in a small amount of water. Ethylenediamine is then added and the titration carried out without the formation of a precipitate.

Dimethylformamide is almost as good a solvent for salts as ethylenediamine. Regarding the solubility of salts in DMF, the following generalities hold:

1. Aromatic and higher aliphatic amine salts of organic and inorganic monobasic acids are soluble.
2. Many ammonium and lower aliphatic amine salts of monobasic acids are also soluble. For example, ammonium nitrate, ammonium bromide, ammonium iodide and ammonium thiocyanate are soluble but ammonium acetate, ammonium chloride and butylamine hydrochloride are insoluble.
3. Salts of most polybasic acids are insoluble.

One disadvantage with dimethylformamide is that water interferes causing high results. If the sample is essentially anhydrous, however, use of DMF is highly recommended.

Salts of ammonia and aliphatic amines give sharp end points in either dimethylformamide or ethylenediamine. Guanidine salts give very poor end points because of the strong base (guanidine) liberated during the titration. Trimethylphenylamonium iodide and other quaternary ammonium salts do not react acidic to azo violet in either DMF or ethylenediamine. Specific examples of salts which have been titrated are given in table 7.

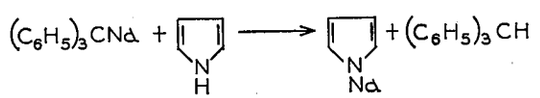
TABLE 7

Titration of Salts with Sodium Methoxide

Salt	Solvent	Indicator
p-Aminophenol hydrochloride	DMF	azo violet
Ammonium benzoate	H_2O-En	azo violet
Ammonium chloride	H_2O-En	azo violet
Ammonium iodide	DMF	thymol blue
Ammonium perchlorate	DMF	thymol blue
p-Bromophenylhydrazine	DMF	thymol blue
Butylamine hydrochloride	H_2O-En	azo violet
Caffeine citrate	DMF	azo violet
Dibutylamine hydrochloride	En	azo violet
Methylamine hydrochloride	En	azo violet
6-Nitroquinoline perchlorate	DMF	thymol blue
Phenanthrene picrate	DMF	thymol blue
m-Phenylenediamine dihydrochloride	H_2O-En	azo violet
Pyridine perchlorate	DMF	thymol blue
Pyridine picrate	DMF	thymol blue
Quinine sulfate	H_2O-En	azo violet

PYRROLES

Pyrroles have extremely weak acidic properties but will form alkali salts under fairly rigorous conditions. Corwin and Ellingson (*57*) used the very powerful base, sodium triphenylmethane to titrate pyrroles as acids. The reaction is:



Sodium triphenylmethane in 1:1 ether-toluene has a deep blood red color. Since all other products are colorless, the titrant serves as its own indicator in much the same manner as permanganate does in redox titrations.

The success of this method depends upon the very careful purification of all solvents used and the complete exclusion of moisture, carbon dioxide and oxygen. For a description of the apparatus and exact procedure employed the original paper should be consulted.

ALCOHOLS

Lithium aluminum hydride reacts readily with alcohols as follows:

$$4ROH + LiAlH_4 \longrightarrow ROLi + (RO)_3Al + 4H_2.$$

Lintner, Schleif and Higuchi (*47*) took advantage of this reaction in developing a rapid method for alcohols. A standard solution of lithium aluminum hydride in tetrahydrofurane (THF) is added in known excess to an anhydrous sample containing the alcohol to be determined. After standing a short period to insure complete reaction, the excess lithium aluminum hydride is back titrated with a standard solution of n-propanol in benzene. The end point is determined electrometrically using a silver or platinum indicator electrode and a remote silver wire surrounded by a solution of lithium bromide and iodine in tetrahydrofurane as the reference electrode. A sharp break of the order of 500 millivolts is obtained at the end point. This is due to the great difference in reducing power of lithium aluminum hydride and aluminum and lithium alkoxides.

PROCEDURE 13

Apparatus

Automatic buret.

Titration vessel of about 125 ml. capacity fitted with openings for buret tip, electrodes and nitrogen flushing.

pH meter or other suitable titrimeter.

Electrodes. The indicator electrode is a silver wire dipping into the solution being titrated. The reference electrode consists of an isolated silver wire surrounded by a solution of lithium bromide and iodine in tetrahydrofurane. Contact between the reference electrode and the main solution is made through a salt bridge of lithium bromide-iodine in tetrahydrofurane.

Reagents

Tetrahydrofurane. Technical grade (du Pont) is distilled twice over lithium aluminum hydride. Since purified tetrahydrofurane forms peroxides rapidly, only a few days' supply is prepared.

Lithium aluminum hydride. A mixture of 25 g. of lithium aluminum hydride and 1 l. of tetrahydrofurane is refluxed for 24 hours. The solution is then decanted and centrifuged and the clear supernatant liquid decanted into a dry bottle. Nitrogen is blown into the bottle after each removal of the reagent to prevent clouding.

n-Butanol. Reagent grade butanol is distilled over sodium and the middle third fraction collected. Exactly 50 g. of butanol is diluted to 1 liter with dry benzene and stored in an automatic buret.

p-Aminoazobenzene. A 0.1% solution in benzene is prepared.

Procedure

The sample is weighed into the dry titration flask. With a stream of nitrogen directed into the flask, 15 ml. of pure tetrahydrofurane and exactly 5 ml. of lithium aluminum hydride solution is pipetted into the flask. After standing 15 to 30 minutes* the mixture is titrated potentiometrically with standard butanol solution.

If desired, 5 drops of p-aminoazobenzene indicator may be added and the end point detected visually. The point at which the indicator remains yellow for 3 minutes is taken as the end point.

A later paper (*58*) showed that visual indicators can be used to detect the end point instead of the potentiometric method. Of the indicators tried, p-aminoazobenzene and several of its derivatives were found to be generally satisfactory but N-phenyl-p-aminoazobenzene gave the sharpest color change.

Lithium aluminum amides of secondary amines can also be used to titrate alcohols and other very weak acids (*48*). The reaction is:

$$ROH + R_2NM \longrightarrow R_2NH + ROM.$$

The end point is detected visually with p-phenylamineazobenzene indicator.

PROCEDURE 14

Reagents

Lithium aluminum amides. An approximately 1 N. solution of lithium aluminum hydride is prepared and standardized as described in procedure 13, page 39. A slight excess of dry di-n-butylamine or piperidine (calculated on a mole for mole basis) is then added and the solution is stored in a light tight bottle under nitrogen.

Preparation of the other reagents required is described in procedure 13, page 39.

Procedure

The sample is weighed into an oven dry 125 ml. flask. A stream of nitrogen is directed into the flask and 15 ml. of pure tetrahydrofurane and exactly 5 ml. of lithium aluminum amide is pipetted. Five drops of p-aminoazobenzene are added and the solution is titrated with standard butanol solution to a permanent yellow color.

Using this procedure several other types of weak acids can be determined. Some examples, taken from the work of Higuchi and Zuck (*48*), are listed in table 8.

Because this method is fairly simple and quick, it should be useful in identification and characterization work. It will first be necessary to do more extensive work showing the stoichiometry of reactions of lithium aluminum amides with carbonyl groups and active hydrogen groups.

* Only 5 minutes is required in many cases.

TABLE 8

Titrations with Lithium Aluminum Amides

Compound	Classification	Equivalents amide/mole
Ethanol	Alcohol	1
n-Pentanol	Alcohol	1
α-Naphthol	Phenol	1
Acetophenone	Ketone	1
Benzophenone	Ketone	1
Benzyl benzoate	Ester	1
Phenyl salicylate	Ester, phenol	2
Acetanilide	Amide	1
Acetamide	Amide	1.2 to 1.3
Carbazole	Active H	1
Phthalimide	Imide	2.2 to 2.5

INTERFERENCES

Very weakly acidic substances such as water and alcohol can usually be tolerated in small amounts but larger concentrations interfere. In ethylenediamine cotaining up to about 5 per cent water or alcohol, very good results are obtained in the titration of carboxylic acids. More weakly acidic compounds give sharp end points only in ethylenediamine which is free of alcohol or water. Samples containing much more than a trace of water give high results when titrated in dimethylformamide. This is probably due to hydrolysis,

$$HCON(CH_3)_2 + H_2O \longrightarrow HCOOH + (CH_3)_2NH,$$

the formic acid formed being titrated along with the acidic constituent of the sample.

Dimethylformamide, ethylenediamine, butylamine and pyridine readily absorb carbon dioxide from the air. A serious error is introduced unless some provision is made to prevent this. It is usually sufficient to carry out the titration in a closed or covered container although for highest precision it is best to work under nitrogen.

Although many acidic compounds containing an ester group can be titrated smoothly, some esters (such as ethyl acetate) cause high results and a fading end point. This is believed to be caused by condensation to form acidic enolic compounds.

$$2CH_3COOEt \xrightarrow{\text{(base)}} CH_3COCH_2COOEt + EtOH.$$

Some halogen containing compounds are dehydrohalogenated by bases. Such compounds interfere causing high results and fading end points.

In a few cases the neutralization product precipitates in a very gelatinous form causing inaccurate results. This can usually be avoided by the proper choice of solvents for the titration.

Titrations using sodium triphenylmethane or lithium aluminum hydride are subject to many additional interferences. Among these are oxygen, aldehydes, ketones and slight traces of water.

PRECISION AND ACCURACY

Most compounds for which the use of sodium methoxide titrant and thymol blue or azo violet indicator is applicable (procedures 9, 10A, 12) can be titrated with an accuracy and precision of ± 0.3 per cent or better. Where o-nitroaniline must be employed as indicator (procedure 10B), the accuracy drops to ± 0.5 or 0.6 per cent. Few data are available regarding the accuracy of potentiometric titrations in ethylenediamine although such titrations should be at least as accurate as those using visual end points. Data given by Higuchi *et al* (*47*) for electrometric titrations with lithium aluminum hydride indicate accuracy of 2 or 3 per cent. In most cases, however, the method would appear to be capable of much greater accuracy. Even with careful technique, accuracy greater than about 5 per cent is doubtful where sodium triphenylmethane is used as the titrant.

V. CONCLUSION

APPLICATIONS

The goal of titrations in nonaqueous solvents is usually to determine the equivalent weight (neutral equivalent) of a pure compound, or else to determine the amount of one or more compounds in a mixture by titrating their acidic or basic groups. The methods described in this booklet are very recent developments for the most part. Nevertheless they have already found considerable use. In the following table are listed some specific applications recently reported by various companies and research workers.

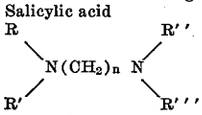
FURTHER WORK NEEDED

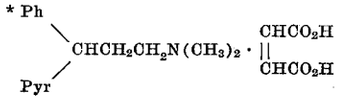
Since a majority of nonaqueous titrimetric methods are of comparatively recent origin, these methods are not on such a firm theoretical basis as might be desired. For example, choice of indicators for use in nonaqueous solvents is still pretty much on a hit-and-miss basis. Fairly intelligent guessing is possible from a glance at pK values in water but many indicators behave entirely differently in nonaqueous solvents. Collection of extensive data on the relative strength of acids and bases (including indicator acids and bases) in nonaqueous solvents would facilitate selection of the proper indicator for any given titration. This might involve the establishment of something analogous to the aqueous pH scale for each major solvent. Such a scale has been established for acetic acid and the pK values for about sixty bases have been measured (*12*). It was found that pK(HAc) and $pK(H_2O)$ are related. This makes it possible to measure the pK value for a weak base in acetic acid and obtain the $pK(H_2O)$ by extrapolation. The pK values of a few indicators have been measured in acetic acid (*11*) but more data of this type is needed.

Lack of fundamental information on electrode systems in nonaqueous solvents has been holding up measurement of acid-base strength and slowing the development of new methods involving potentiometric titrations. Many of the electrodes now used will give an indication of the proper end point but the potentials obtained cannot be reproduced. This is particularly true for titrations in basic solvents such as butylamine and ethylenediamine. In many cases the potentiometric curve indicates a much smaller break at the end point than ought to be the case as evidenced by the sharp indicator end point.

Finally it appears that new indicators should be developed for use in nonaqueous solvents. Over five hundred acid-base indicators are

TABLE 9

Compound Determined	*Sample*	*Solvent*	*Remarks*
Phenols and Phenolic groups	Lignin	En, Morpholine, Pyridine	
Salicylic acid	Degradation product	Benzene-EtOH	
	Pure compound	Dioxane	Determined neutral equivalent
Imidazole	Pure compound	HAc	Determined neutral equivalent
Chrysanthemum carboxylic acid	Product of hydrolysis	Pyridine	MeONa in pyridine used as titrant
Unsaturation	C = C ester	HAc	Used HBr in HAc, backtitrated excess
Sodium nitrobenzoate	Technical grade (85%)	Dioxane	
Sarcosine nitrile	Crude mix	HAc	
2-Alkylimidazolines	Purified	HAc	
β-Alanine derivatives	Purified	HAc	
Hydrogen chloride	Chlorinated hydrocarbons	Benzene	Added triphenylguanidine and backtitrated excess
Pyrazine derivatives	Research intermediates	Dioxane, HAc	
Trimeton maleate*	Antihistamines	HAc	
dl-Lysine dihydrochloride	Pure product	HAc	$HgAc_2$ added to combine with the HCl
Wool wax acid	Pure product	Benzene-methanol	Determined neutral equivalent
Morphine, codeine	Pure chemicals, pharmaceuticals	Dioxane, HAc	
Pyridine	Impure pyridine	Dioxane	
Barbiturates	Tablets	DMF	
Sulfonamides	Tablets	DMF	
1,3-Diketones	Research compounds	DMF	Neutral equivalents determined
N-Methylaniline	Mixture with N-methyl (2,4-dinitrophenyl) aniline	HAc	



available but only a few of these can be used in acidic solvents such as acetic acid or in basic solvents such as butylamine, pyridine and ethylenediamine. Ideally, indicators with different transition ranges should be available so that the complete acidity scale in each solvent would be covered.

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