CHAPTER 5

# Acidimetry and Alkalimetry

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One of the fundamental procedures in analytical chemistry is *volumetric* or *titrimetric* analysis. By definition this involves the determination of the amount of substance by measuring the volume of a solution of a second substance necessary to react completely with the substance being analyzed. The process is known as *titration*, and the volume of solution or *titrant* consumed in the titration contains a chemically equivalent amount of reactant as the substance being analyzed. A titrant which contains a known

amount of reactant in each unit of volume is a *standard solution*. In the titration process the standard solution is usually added from a burette into a suitable size beaker or flask containing the solution of the substance to be analyzed. The solution is stirred manually or mechanically during the titration. Provision must be made for detecting the point at which sufficient standard solution has been added to react completely with the substance being analyzed. This may be accomplished by adding to the titration flask an agent which changes color when the reaction is complete, or it may be realized by recording the voltage changes in the solution as titrant is added. For this purpose, a pH meter, a potentiometer, an automatic titrator or similar electronic device may be employed. The *end point* occurs when sufficient titrant has been added to effect a change in indicator color or to produce a response by the electronic method which signals the completion of the reaction. The latter technique is advantageous where the solution is colored, turbid, or where more than one endpoint is expected. The *equivalence point* or *stoichiometric point* is the theoretic point at which the reaction is complete or when exactly equivalent amounts of the two reactants have been mixed. Ideally, the end point and the stoichiometric point should be identical, but for a number of reasons this is not always possible.

This chapter is concerned with *neutralization* reactions and covers both *acidimetry* and *alkalimetry*. Acidimetry involves the determination of acidic substances by titration with a standard base solution, and alkalimetry is the measurement of basic substances by titration with a standard acid. Neutralization reactions represent one aspect of volumetric analysis. Others include oxidation-reduction and volumetric precipitations. These are discussed elsewhere in this text. This presentation will be limited to those reactions involving water as the solvent. Thus, *acid* and *base* are defined according to the Arrhenius theory of acids and bases. An acid is any substance which in water ionizes to give hydrogen ions (hydronium ions*):

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

A base is any substance which in water ionizes to give hydroxyl ions:

$$BOH \rightleftharpoons OH^- + B^+$$

Thus, neutralization is the combination of the proton and hydroxyl ion to form the water molecule. A salt is the by-product of this reaction

$$H_3O^+A^- + B^+OH^- \rightleftharpoons 2H_2O + AB$$

or, simply,

$$H_3O^+ + OH^- \rightleftharpoons 2H_2O$$

Therefore, it may be stated that all acidimetric and alkalimetric reactions covered here involve the neutralization of protons or hydroxyl ions by an equivalent amount of the opposite species. To be sure, the concept of acids

* Although frequently referred to as a proton ($H^+$), it is generally considered to exist in solution as the hydrated ion or hydronium ion ($H_3O^+$).

and bases has been extended to include solvents other than water, acids other than proton donors, and bases other than hydroxyl ions donors. These are considered in Chapter 6, on nonaqueous titrimetry.

## 5.1 CONCENTRATION OF SOLUTIONS

The concentration of solutions used in quantitative analysis is expressed in various ways. Per cent weight in weight or per cent weight in volume is used for denoting the concentration of solute in reagent solutions used in the preparation of standard solutions. It is used also for test solutions (T.S.). For example, hydrochloric acid, USP, contains about 37%, by weight, HCl. Hydrochloric acid, diluted, USP, is a 10% solution, weight in volume. Phenolphthalein test solution, USP, is a 1% solution in alcohol, weight in volume. Per cent weight in weight or weight in volume means grams per 100 g of solution, or grams per 100 ml of solution, respectively. Concentration is frequently expressed as milligrams per milliliter of solution, which has the same numerical value as grams per liter. Although infrequently used in quantitative analysis, milligram per cent indicates the number of milligrams per 100 ml of solution.

The concentration of a standard solution may be expressed in terms of molarity or the number of moles of solute in each liter of solution. A molar solution contains 1 gram-molecular weight (1 mole) of solute in each liter of solution. The molarity is designated by the abbreviation *M* preceded by a numerical value indicating the number of moles per liter. To illustrate, 0.1 *M* HCl solution contains $\frac{1}{10}$ mole or 3.65 g of HCl per liter. The number of moles of solute in a given volume of solution is calculated by Eq. (5.1).

$$\text{number of moles} = \text{volume (liters)} \times \text{molarity (moles/liter)} \qquad (5.1)$$

The molarity of a solution is independent of the reaction in which the solute is involved, and in quantitative analysis it is commonly used where a reagent may undergo several possible reactions depending upon conditions. An illustration is 0.05 *M* potassium iodate solution, a reagent employed in oxidation-reduction procedures.

Another useful expression permits the calculation of the number of moles from the grams of a solute:

$$\text{number of moles} = \frac{\text{grams of solute (g)}}{\text{molecular weight (mol. wt.)}} \qquad (5.2)$$

By combining expressions (5.1) and (5.2), a fundamental relationship is obtained:

$$\text{weight of solute (g)} = \text{volume (liters)} \times \text{molarity (moles/liter)} \times \text{mol. wt.} \qquad (5.3)$$

These relationships should be memorized by the student, but it is even more important that they be thoroughly understood. They are helpful in solving all problems dealing with molar solutions.

The use of molarity as an expression of concentration permits the comparison of solutions on the basis of molecules of solute present. In other words, equal volumes of all solutions having the same molarity contain the same number of molecules of solute. It does not take into account the ratio in which molecules react with one another.

Since volumes in quantitative analysis usually involve milliliters (ml) instead of liters, it is more convenient to have a smaller unit than the mole. For this reason the millimole (mM) is frequently used. One mM equals 0.001 mole and is defined as the molecular weight of the solute in milligrams. The molarity of a solution can be expressed as the numbe. of millimoles per milliliter of solution. A 1.0 *M* solution contains one molecular weight of solute in milligrams in each milliliter.

This gives rise to the following relationship:

$$\text{mg solute} = \text{volume (ml)} \times \text{molarity (mM/ml)} \times \text{mol. wt.} \qquad (5.4)$$

A *molal* solution contains 1 mole of solute in each 1000 g of solvent. The symbol *m* designates molality. Since volume concentrations are used in all quantitative procedures, this method of expressing concentration is not of importance here, but it does have application in physicochemical calculations.

The use of molarity in expressing concentration, as indicated earlier, is not based on the reaction in which the solute is involved and, therefore, does not permit a direct comparison of strength with other solutions. A 1.0 *M* sodium hydroxide solution will neutralize an equal volume of 1.0 *M* hydrochloric acid solution, since the reaction which takes place is mole for mole, but it will neutralize only one-half its volume of 1.0 *M* sulfuric acid solution This is illustrated by the following equations:

$$NaOH + HCl = NaCl + H_2O$$
$$2NaOH + H_2SO_4 = Na_2SO_4 + 2H_2O$$

Since sulfuric acid has two replaceable hydrogens, two molecules of sodium hydroxide will react with each molecule of sulfuric acid. For phosphoric acid, one, two, or three hydrogens may be involved in the reaction with sodium hydroxide.

In volumetric analysis it is important to be able to express the concentration of a solution in terms of its ability to neutralize the opposite species. The *equivalent weight* (equiv. wt.) of a substance is based upon the reaction in which it is involved. In neutralization reactions, the equivalent weight is defined as that quantity of acid or base which will furnish or react with 1 gram-atomic weight (1.008 g) of hydrogen ion. For acids it is the molecular weight divided by the number of hydrogens which are replaced or neutralized. Thus the equivalent weight of hydrochloric acid is the same as the molecular weight, and for sulfuric acid it is the molecular weight divided by 2. However, the equivalent weight of phosphoric acid may be the molecular weight or one-half or one-third the molecular weight, depending on the reaction involved in

the neutralization. If phosphoric acid is titrated to the first end point (Methyl Orange), the equation for the reaction is

$$H_3PO_4 + NaOH = NaH_2PO_4 + H_2O$$

and the equivalent weight is the same as the molecular weight. If it is titrated to the second end point (phenolphthalein), the equation becomes

$$H_3PO_4 + 2NaOH = Na_2HPO_4 + 2H_2O$$

and the equivalent weight is then one-half the molecular weight. If all three hydrogens are replaced

$$H_3PO_4 + 3NaOH = Na_3PO_4 + 3H_2O$$

the equivalent weight is one-third the molecular weight. In most instances the reaction involved in neutralization is obvious, and does not have to be specified to determine the equivalent weight.

For bases, the equivalent weight is the molecular weight divided by the number of hydrogen atoms it is capable of neutralizing. The equivalent weight of sodium hydroxide is the same as the molecular weight, and that of barium hydroxide is one-half the molecular weight. The equivalent weight of sodium carbonate may be the same as the molecular weight or one-half the molecular weight, depending on the reaction involved in the neutralization. If sodium carbonate is neutralized to the first end point (phenolphthalein)

$$Na_2CO_3 + HCl = NaHCO_3 + NaCl$$

the equivalent weight is the same as the molecular weight. If, on the other hand, it is completely neutralized according to the equation

$$Na_2CO_3 + 2HCl = H_2O + CO_2 + 2NaCl$$

the equivalent weight is one-half the molecular weight.

The equivalent weight of a salt, in general, is determined from the number of replaceable hydrogens which were involved in its formation. For NaCl it is the same as the molecular weight; for $BaSO_4$, it is one-half the molecular weight; and for $Al_2(SO_4)_3$, it is one-sixth the molecular weight.

Since 1 equiv. wt. of an acid will neutralize 1 equiv. wt. of base (each furnishes or reacts with the same quantity of hydrogen ion), a convenient method is provided for expressing the concentration of acids and bases on comparable terms. A *normal* solution contains 1 equiv. wt. in each liter of solution The symbol *N* preceded by a numerical value is used to indicate the normality of a solution. A solution which contains 3.65 g of hydrogen chloride in 1 liter is 0.1 *N* in HCl, since it contains 0.1 equiv in 1 liter of solution. (The designation of *N*/10 HCl may also be used in this case.)

Equation (5.5) summarizes the important relationships involving equivalents. Since 1 liter of a 1 *N* solution contains 1 equiv. wt. of solute, 1 ml of

$$\text{number of equiv} = \text{volume (liters)} \times \text{normality (equiv/liter)} = \frac{\text{g solute}}{\text{equiv. wt.}} \tag{5.5}$$

this solution will contain 0.001 equiv or 1 meq (milliequivalent). There are 1000 meq in 1 equiv. It was indicated previously that a mole is the molecular weight in grams and a millimole is the molecular weight in milligrams. Likewise, the equivalent weight of a solute is expressed in grams and the milliequivalent weight is indicated in milligrams. Also, if the volume is in liters, calculations are usually in equivalents and grams, whereas milliequivalents and milligrams are used when the unit of volume is the milliliter. Normality refers to the number of equivalents per liter of solution or the number of milliequivalents per milliliter of solution. Since most volumetric work involves milliliters rather than liters, the milliequivalent weight is used more frequently than the equivalent weight.

The normality of a solution is a simple whole number multiple of the molarity, since the number of equivalents in a mole of solute is obtained by dividing the molecular weight by the number of hydrogens furnished or neutralized.

The number of milliequivalents of an acid will exactly equal the number of milliequivalents of a base needed to neutralize the acid

$$\text{meq (acid)} = \text{meq (base)} \tag{5.6}$$

The volume and normality of the acid may also be related to the milliequivalents of base:

$$\text{ml} \times N\,\text{(acid)} = \text{meq (base)} \tag{5.7}$$

Finally, the volumes and normalities of base and acid may be equated:

$$\text{ml} \times N\,\text{(acid)} = \text{ml} \times N\,\text{(base)} \tag{5.8}$$

Equations (5.6), (5.7), and (5.8) are of vital importance in calculations involving neutralization reactions.

In the official compendia it is the practice to express the equivalency of a standard solution with the amount of substance under assay. This is known as the *titer* value, or the number of milligrams of substance equivalent to 1 ml of a standard solution (1 *N*, 0.1 *N*, etc.). For example, in the assay of acetic acid, USP, the titer value as stated in the monograph is, "Each ml of 1 *N* sodium hydroxide is equivalent to 60.06 mg of $C_2H_4O_2$." The milligram value is the product of the normality of the titrant and the milliequivalent weight of the substance assayed. The meq. wt. of acetic acid is 60.05 mg, and the sodium hydroxide solution is 1 *N*. If the standard solution specified in the assay were 0.1 *N*, the titer value would be 60.05 × 0.1 or 6.005, or each milliliter of 0.1 *N* sodium hydroxide would be equivalent to 6.005 mg of acetic acid. In practice the actual normality of the sodium hydroxide solution may not be exactly 1 *N* but may be, for example, 0.975 *N*. Thus, in calculating the acetic acid content in a weighed sample taken for analysis, the volume of 0.975 *N* sodium hydroxide necessary to neutralize the acid is determined. This volume may be converted to the equivalent volume of a 1 *N* solution by using Eq. (5.8). This would have been the volume obtained if a

1 *N* solution of sodium hydroxide were used in the titration. The titer value may now be employed to calculate the milligrams of acetic acid in the sample taken for analysis. This value multiplied by 100 and the product divided by the sample weight yields the per cent content. Alternatively, it would be just as correct to use the product of the actual volume and normality of the sodium hydroxide solution, since according to Eq. (5.7), the milliequivalents of the base titrant are exactly equal to the milliequivalents of the acid being determined. The calculations would be derived from

$$\frac{\text{ml NaOH} \times 0.975 \times \text{meq. wt. } C_2H_4O_2 \times 100}{\text{sample wt.}} = \%\, C_2H_4O_2$$

The following are typical problems which illustrate how the relationships derived in the previous section may be applied.

EXAMPLE 1. How many grams of $H_2SO_4$ (95%) are needed to prepare 600 ml of a 0.1 *M* solution?

*Solution:* Equation (5.1) is used. The moles of $H_2SO_4$ needed equals the volume times the molarity or

$$\text{moles } H_2SO_4 = 0.6 \text{ liter} \times 0.1 \text{ mole/liter} = 0.06 \text{ mole}$$

Since 1 mole = 98.08 *g*, 0.06 mole = 5.88 g. Therefore, 5.88/0.95 = 6.19 g of 95% $H_2SO_4$ which, dissolved in 600 ml of water, will give a 0.1 *M* solution.

EXAMPLE 2. If a solution of HCl contains 3.65 g of hydrogen chloride in a liter, how many millimoles are there in each milliliter of solution?

*Solution:* Equation (5.2) is used. Since the mol. wt. of HCl is 36.5, 1 liter of the solution contains 3.65/36.5 or 0.1 mole and is 0.1 *M*. It therefore contains 100 millimoles of HCl in a liter or 0.1 millimole in each milliliter.

EXAMPLE 3. How many milligrams of hydrochloric acid are there in 100 ml of a 0.5 *M* solution?

*Solution:* Refer to Eq. (5.4):

$$\text{mg solute} = \text{ml solution} \times M \times \text{mol. wt.}$$

$$= 100 \times 0.5 \times 36.5$$

$$= 1825 \text{ mg or } 1.825 \text{ g}$$

There are 100 × 0.5 or 50 millimoles of HCl and since a millimole is 36.5 mg, there are then 50 × 36.5 or 1825 mg of HCl in 100 ml of this solution.

EXAMPLE 4. What is the normality of a solution which contains 7.500 g of $H_2SO_4$ in 1.5 liters of solution?

*Solution:* See Eq. (5.5):

$$\text{volume} \times \text{normality} = \frac{\text{g solute}}{\text{equiv. wt.}}$$

$$1.5 \times N = \frac{7.500}{49.04}$$

$$\frac{7.500}{49.04 \times 1.5} = 0.1019 \text{ equiv/liter}$$

*Note:* Care must be exercised to use the proper units. When the volume is expressed in liters, the weight of solute should be in grams. When the volume is in milliliters, the weight should be in milligrams. Equivalent weight is expressed in grams and the milliequivalent weight is expressed in milligrams. The student must be careful not to mix units.

EXAMPLE 5. How many milliequivalents of hydrogen chloride are there in 200 ml of a 0.2500 *N* solution? How many milligrams of hydrogen chloride does this represent?

*Solution:* Refer to Eq. (5.5) and (5.7):

$$\text{meq} = \text{ml} \times N$$

$$= 200 \times 0.2500$$

$$= 50 \text{ meq HCl}$$

$$= \frac{\text{mg solute}}{\text{meq. wt.}}$$

$$\text{mg solute} = \text{meq} \times \text{meq. wt.}$$

$$= 50 \times 36.5$$

$$= 1825 \text{ mg HCl}$$

EXAMPLE 6. What volume of a 0.2500 *N* acid solution is needed to prepare 1 liter of a 0.1000 *N* solution?

*Solution:* Equation (5.8) is applied:

$$\text{volume} \times \text{normality (acid A)} = \text{volume} \times \text{normality (acid B)}$$

$$\text{liters} \times 0.2500 = 1 \times 0.1000$$

$$\text{volume of acid A} = 0.4 \text{ liter or } 400 \text{ ml}$$

*Note:* The equivalents of acid in the final solution must come from a calculated volume of the original solution. A liter of a 0.1000 *N* solution contains 0.1 equiv of acid. Since 1 liter of the original solution contains 0.2500 equiv, 400 ml contains 0.1 equiv of acid. In preparing this solution exactly 400 ml of the original solution is diluted to exactly 1 liter to produce a 0.1000 *N* solution.

EXAMPLE 7. What is the normality of a base, if 35.00 ml is required to neutralize exactly the monobasic acid, potassium acid phthalate, in a sample weighing 625.2 mg? The milliequivalent weight of KHP is 204.2 mg/meq.

*Solution:* Equation (5.5) applies:

$$\text{ml} \times N = \text{meq} = \frac{\text{mg solute}}{\text{meq. wt.}}$$

$$35.00 \times N = \frac{625.2}{204.2}$$

$$N = 0.08747 \text{ meq/ml or equiv/liter}$$

EXAMPLE 8. What is the normality of an acid solution if 25.50 ml is necessary to neutralize 20.00 ml of a 0.1106 *N* base solution?

*Solution:* Refer to Eq. (5.8):

$$\text{ml} \times N = \text{ml} \times N$$

$$25.50 \times N = 20.00 \times 0.1106$$

$$N = 0.08674 \text{ equiv/liter}$$

EXAMPLE 9. A sample of sodium borate, $Na_2B_4O_7 \cdot 10H_2O$, mol. wt. 381.4, weighing 2.8504 g is assayed by dissolving in 50 ml water and titrating to a methyl red end point with 0.5 *N* HCl. The titration required 28.96 ml. What is the per cent purity of the sodium borate?

*Solution:* Since sodium borate is a salt derived from an acid having two replaceable hydrogens, the equivalent weight is one-half the molecular weight or 190.7. The milligrams of sodium borate is calculated by applying Eq. (5.5):

$$\text{mg solute} = \text{ml} \times N \times \text{equiv. wt.}$$

$$= 28.96 \times 0.5 \times 190.7$$

$$= 2761.3 \text{ mg or } 2.7613 \text{ g}$$

$$\% \text{ purity} = \frac{\text{g solute}}{\text{sample wt.}} \times 100 = \frac{2.7613}{2.8504} \times 100 = 96.88\%$$

EXAMPLE 10. What is the normality of hydrochloric acid, 36% w/w, having a specific gravity 1.18?

*Solution:* Each 100 g of solution contains 36 g of HCl. Therefore, each gram of solution contains 360 mg of HCl. Since the specific gravity is 1.18, 1 g of solution is 1/1.18 or 0.847 ml:

$$\text{ml} \times N = \frac{\text{mg solute}}{\text{meq. wt.}}$$

$$0.847 \times N = \frac{360}{36.5}$$

$$N = 11.65 \text{ meq/ml}$$

## 5.2 STANDARDIZATION OF SOLUTIONS

The process of determining the exact strength of a standard solution is known as standardization and may be accomplished in several ways. Certain standard solutions used in volumetric analysis can be prepared by weighing an exact amount of reagent chemical to give a desired normality or molarity. An accurately weighed amount of the chemical is transferred to a volumetric flask and diluted to the mark with solvent. This is possible only if the solute is obtainable in a highly purified state, is stable, and is not hygroscopic. This procedure is not generally used in preparing standard solutions of acids and bases.

The usual technique is to weigh an amount of solute approximating the exact quantity which, upon dissolving in water, will give the desired normality. The solution is then standardized by one of the methods to be discussed later. The exact normality and date of analysis are placed on the label of the container. In certain instances, such as for standard solution of sodium hydroxide, it is necessary to restandardize the solution at frequent time intervals to correct for changes in normality resulting from absorption of carbon dioxide from the air. The problem can be minimized in this instance by protecting the solution from carbon dioxide by using soda-lime absorption tubes. Standard solutions of acids such as hydrochloric acid and sulfuric acid are stable, and frequent restandardization is usually not necessary. If a solution of definite normality is required, such as exactly 0.1 $N$ sulfuric acid, a solution is prepared which is slightly stronger than 0.1 $N$. The solution is standardized, and then diluted with the exact volume of water to produce the desired normality. The expression

$$\text{ml} \times N(\text{acid}_1) = \text{ml} \times N(\text{acid}_2)$$

which is a modification of equation (5.8), is used to calculate the final volume of the solution which has the desired normality. The final solution is then standardized.

The exact normality of a standard solution may be determined by titrating the solution against a known weight of a *primary standard*. A primary standard is a white crystalline solid which is not hygroscopic; it is a substance of extremely high purity, is of known composition, is stable to air and light, and is capable of being dried at 110° without decomposition. In addition it should dissolve readily in water and should react quantitatively with the solute in the titrant being standardized. Ideally, it should have a high equivalent weight. This will reduce errors in weighing. The error in weighing may amount to 0.2 mg and thus a sample weight of 200 mg will assure an accuracy of 1 part in 1000. Since the usual burette has a capacity of 50 ml, a titration should consume between 30 and 40 ml to minimize errors in reading the burette. If the equivalent weight is low, a smaller weight of substance will be

required to consume the ideal volume of titrant. Primary standards are available from the National Bureau of Standards, Washington, D.C., or from chemical supply houses.

In standardizing a solution, an accurately weighed sample of the primary standard (the amount necessary to consume 30 to 40 ml of titrant) is dissolved in water and titrated to the end point with the solution being standardized. The volume of water used to dissolve the primary standard is not critical, since the total milliequivalents of the standard will be the same regardless of the volume of the solution. From the volume of titrant consumed, the sample weight of primary standard, and its equivalent weight, the normality of the standard solution is readily calculated by using Eq. (5.5). It should be emphasized that in all quantitative procedures an accuracy of at least 1 part in 1000 should be maintained. Therefore, weighings should be carried out to the fourth decimal place, and burette readings should be made to the nearest 0.02 ml.

There are a number of suitable primary standards available for standardizing solutions of acids and bases. Several are noted briefly here.

*Sulfamic acid*, $HSO_3NH_2$, equiv. wt. 97.09, is a white crystalline solid, a strong monobasic acid, and is readily prepared in a highly purified state. It is water soluble, stable up to a temperature of 130°, and highly recommended as a primary standard for solutions of bases.

*Potassium acid phthalate*, $KHC_8H_4O_4$, equiv. wt. 204.22, is a white crystalline solid, stable on drying at 110°, water soluble, and obtainable in pure form. Its high equivalent weight is a definite advantage. It is a weak monobasic organic acid comparable in strength to acetic acid and therefore can be titrated only with strong bases. This is not a disadvantage, since base titrants are always strong and are usually employed in the determination of weak acids. Phenolphthalein is the indicator when this standard is employed.

*Potassium acid iodate*, $KH(IO_3)_2$, equiv. wt. 389.94, is a white crystalline solid, stable at 110°, anhydrous, nonhygroscopic, and a strong acid. It is available in purity suitable for use as a primary standard for solutions of bases.

*Sodium carbonate*, $Na_2CO_3$, equiv. wt. 106.00 or 53.00, can be obtained in a high state of purity. When used as a primary standard, sodium carbonate should be heated at 270° to convert to the carbonate any sodium bicarbonate which may be present as an impurity and to remove moisture completely. Sodium bicarbonate may be used to prepare this standard by heating at 270° until constant weight is attained. Sodium carbonate is water soluble, readily available, and an excellent primary standard for solutions of acids.

In standardizing a solution, the primary standard should be selected which most closely approximates the type of substance for which the solution is to be used for analysis. For example, if a base is to be used for the analysis of weak acids such as acetic acid, the primary standard should be potassium acid

phthalate. If an acid solution is to be used for the determination of carbonates, sodium carbonate would be appropriate as a primary standard.

When an acid or base solution has been standardized against a primary standard, its exact concentration is known, and it now can be used to standardize other solutions. It then is referred to as a *secondary standard.* An exact volume of the secondary standard is titrated with the solution to be standardized. For example, a solution of sodium hydroxide can be very simply standardized by determining the volume necessary to neutralize 25 ml of a hydrochloric acid solution whose normality has been determined against a primary standard. Equation (5.8) is applied. Since additional errors are introduced when a secondary standard is used for standardization, for analyses requiring the greatest accuracy, it is advisable to resort to primary standards for standardizing all titrants.

Hydrochloric acid and sulfuric acid solutions can be standardized by *gravimetric standardization.* For hydrochloric acid, the chloride ion in a measured volume of the solution is quantitatively precipitated as silver chloride, which is dried and weighed. From the weight of the precipitate, the amount of hydrochloric acid in the sample taken for analysis is calculated, and from this the normality is determined with Eq. (5.5). To illustrate, 25 ml of a solution of hydrochloric acid produced, after treatment with silver nitrate, a precipitate which weighed 3.5250 g after drying to constant weight. Since each mole of AgCl is equivalent to 1 mole of HCl, the amount of HCl represented by the precipitate is readily calculated by multiplying the weight by the gravimetric factor. This will give the weight of HCl in 25 ml of the solution. Equation (5.5) can then be used to determine the normality. However, it is simpler, and just as correct, to calculate the equivalents of AgCl in the precipitate. This must equal the equivalents of HCl in the original 25-ml aliquot of the solution. Thus,

$$\frac{\text{wt AgCl}}{\text{equiv. wt. AgCl}} = \frac{3.5250}{143.34} = 0.0246 \text{ equiv AgCl or HCl/25 ml}$$

$$0.0246 \times 40 = 0.9840 \text{ equiv/liter} = \text{normality}$$

In a like manner, a solution of sulfuric acid may be standardized by precipitating the sulfate ion in a measured volume as barium sulfate, then drying and weighing.

## 5.3 SELECTION OF A TITRANT

The choice of the acid or base for the titrant in a neutralization reaction is rather limited. The standard acid solution is usually hydrochloric acid or sulfuric acid; the standard base solution is usually sodium hydroxide, although potassium hydroxide and barium hydroxide may also be employed. Several characteristics must be considered in the selection of an acid or base

as a suitable titrant. The acid or base should be strong so that even weak acids and bases can be titrated visually with a readily detectable end point. It should be sufficiently water soluble to permit the preparation of solutions up to 1 *N* in strength. For most titrimetric procedures concentrations of 0.1 to 1.0 *N* are used, although concentrations as low as 0.01 *N* can be employed for visual titrations. Titrations with concentrations of titrant as low as 0.001 *N* can be effected potentiometrically. Standard solutions should be stable under usual laboratory conditions and, ideally, it should not be necessary to re-standardize the solution at frequent intervals. Oxidizing or reducing agents are undesirable as acid-base titrants, since they may react with the substance under analysis in an untoward manner. They may react with extraneous organic matter or even with oxygen in the air to alter the normality of the solution, and they are likely to react with the indicator, thus interfering with end-point detection. Volatile compounds such as ammonia are not desirable as titrants, since they are difficult to preserve without elaborate precautions. Their salts should be soluble, since the formation of a precipitate during the titration may obscure the end point.

Most chlorides are water soluble. Hydrochloric acid is ideal as an acid titrant, and in general, it is inert to oxidation and reduction. Even though hydrogen chloride is a gas, it is highly ionized in aqueous solutions and its partial pressure is so low that a 0.1 *N* solution can be boiled for a considerable period of time without appreciable loss of acid. Sulfuric acid is nonvolatile but does form insoluble salts with alkaline earth hydroxides. However, as an acid titrant it is as useful as hydrochloric acid. Nitric acid is undesirable because of its oxidizing properties.

Sodium hydroxide is the most frequently used basic titrant. Potassium hydroxide offers no advantage and is somewhat more expensive. Barium hydroxide is poorly soluble and permits the preparation of solutions no more concentrated than 0.05 *N*. Since these reagents are strong bases, they tend to absorb carbon dioxide from the atmosphere and to form the corresponding carbonate. This is not a serious matter if the solution is to be used for the titration of strong acids. However, when the standard alkali solution is used for analysis of weak acids or when it is 0.05 *N* or less, carbonate formation must be avoided.

Carbonate formation with barium hydroxide is not a problem because barium carbonate is insoluble. However, it will reduce the concentration of the solution, necessitating restandardization. Alkali solutions should, as a rule, be prepared carbonate-free and should be protected at all times from carbon dioxide by means of soda-lime absorption tubes. In the preparation of standard solutions carbonate may be removed by either of two methods. A simple technique for sodium hydroxide is first to prepare a concentrated solution (about 50%). The carbonate which is only slightly soluble under such conditions is removed by filtration through a Gooch crucible or by decantation of the clear solution above the residue. The clear concentrate may

now be diluted with carbon dioxide-free water to the desired concentration. This procedure is not applicable for solutions of potassium hydroxide, since potassium carbonate is soluble in concentrated potassium hydroxide. By a second method, barium chloride or barium hydroxide solution is added in slight excess to the solution of sodium hydroxide or potassium hydroxide. After the precipitate has settled completely, the clear solution is filtered into a suitable container. All standard alkali solutions should be restandardized frequently.

Standard solutions of sodium hydroxide may be prepared through the aid of anion exchange resins. Davies and Nancollas[1] passed the base solution through a column of Amberlite IRA-400. Carbonate remained on the column while the hydroxide appeared in the eluate. Steinbach and Freiser,[2] using the same resin, prepared standard sodium hydroxide by passing a solution containing a calculated amount of sodium chloride through the resin column. Chloride ion remained on the column, while sodium hydroxide appeared in the eluate which was diluted to a definite volume. The solution was carbonate-free.

### Preparation of 0.1 *N* Hydrochloric Acid Solution

Approximately 1 liter of distilled water is added to a clean glass-stoppered bottle. About 8.3 ml of reagent-grade concentrated hydrochloric acid is measured with a graduated cylinder and transferred to the bottle. The bottle is stoppered and the solution is mixed by shaking the bottle for several minutes. Commercial concentrated hydrochloric acid has a specific gravity of 1.18 and contains about 37% hydrogen chloride by weight. A 0.1 *N* solution should contain 3.65 g of HCl in 1 liter of solution. Since each gram of concentrated solution represents 0.37 g of HCl, then 9.86 g of concentrate contains 3.65 g of HCl, or the amount needed for 1 liter of a 0.1 *N* solution. It is more convenient to measure a volume than a weight of solution. Thus,

$$\frac{\text{wt.}}{\text{sp. gr.}} = \text{volume}, \quad \text{or} \quad \frac{9.86}{1.18} = 8.3 \text{ ml}$$

is the volume of concentrated solution needed. The solution is standardized by one of the methods described earlier, or by the specific directions given here, using sodium carbonate as the primary standard.

About 2 g of sodium carbonate, anhydrous and reagent-grade, is dried in a porcelain dish by heating in an oven at 270° for about 1 hr and then allowing it to cool in a desiccator. Alternatively, an equivalent quantity of pure sodium bicarbonate may be heated at 270° until constant weight is attained. Three samples of sodium carbonate, between 0.16 and 0.20 g, are accurately weighed and transferred to 250-ml Erlenmeyer flasks. Each is dissolved in about 100 ml of distilled water, and 2 drops of methyl orange indicator

solution are added. The flasks are shaken until the sodium carbonate has dissolved completely. The hydrochloric acid solution which is to be standardized is added to a 50-ml burette and each sodium carbonate sample is titrated with the acid solution to the point where the yellow solution shows a faint pink color. The inside wall of the flask is washed with water by means of a wash bottle. If the solution shows a yellow color again, add acid from the burette until the faint pink color is restored. From the volume of acid consumed and the weight of the sodium carbonate sample, the normality of the hydrochloric acid is calculated to four significant figures using Eq. (5.5). Since titration is carried to the methyl orange end point, the equivalent weight for the sodium carbonate is 53.00. The three results should show an average deviation of less than 1 part per thousand.

### Preparation of 0.1 *N* Sodium Hydroxide Solution

Dissolve 4.2 g of sodium hydroxide, sticks or pellets, in 400 ml distilled water. Add dropwise with stirring, saturated barium hydroxide solution until precipitate ceases to form (about 2 to 3 ml) or add 10 ml of 0.25 *M* barium chloride solution. Allow to stand until precipitate subsides. Decant or filter the clear supernatant liquid into a hard-glass bottle. It is advisable to coat the inside surface of the bottle with a thin layer of paraffin. This will prevent the alkali from attacking the glass. The bottle should be tightly stoppered with a rubber stopper, since the alkali may cause a glass stopper to freeze to the bottle. The solution may be standardized against the hydrochloric acid solution which was standardized against a primary standard. Exactly 25 ml of 0.1 *N* hydrochloric acid is transferred by pipette to a 250-ml Erlenmeyer flask. About 50 ml of carbon dioxide-free distilled water is added to the flask, 2 drops of phenolphthalein indicator solution are then added, and the solution is titrated with the sodium hydroxide solution to the first permanent pink coloration. From the volume and normality of the acid solution and the volume of the base consumed, the exact normality of the base is determined using Eq. (5.8). The standardization is repeated twice, and the average of the three results is accepted as the normality of the solution. The average deviation should not be greater than 1 part per thousand.

The base solution may also be standardized against potassium acid phthalate (KHP). Three samples of pure and dried KHP, between 0.5 and 0.8 g, are accurately weighed and transferred to 250-ml Erlenmeyer flasks. About 100 ml of distilled water is added, and the flasks are shaken until the KHP has dissolved. Two drops of phenolphthalein indicator solution are added, and the samples are titrated with the sodium hydroxide solution to the first permanent pink color. One drop of titrant should produce the end-point color change. From the weight of KHP sample, its equivalent weight, and the volume of base consumed in the titration, the exact normality of the base is calculated by using Eq. (5.5). The average deviation should be better than 1 part per thousand.

## 5.4 INDICATORS

Indicators for neutralization reactions are highly colored organic dyes capable of exhibiting a reversible change in color over a narrow range in pH. The pH range over which this color transition occurs varies for the different indicators. Typical indicators used in acid-base titrations are listed in Table 5.1. The acid and base colors and the pH range over which the color change

TABLE 5.1: Indicators Used in Acid-Base Titrations

| Indicator | pH range | Acid color | Base color | $pK_{ind}$ |
|---|---|---|---|---|
| Cresol red | 0.2–1.8 | Red | Yellow | |
| Thymol blue | 1.2–2.8 | Red | Yellow | 1.7 |
| Methyl yellow | 2.9–4.0 | Red | Yellow | 3.3 |
| Bromophenol blue | 3.0–4.6 | Yellow | Blue | 4.1 |
| Methyl orange | 3.1–4.4 | Red | Yellow | 3.7 |
| Methyl red | 4.2–6.3 | Red | Yellow | 5.0 |
| Chlorophenol red | 4.8–6.4 | Yellow | Red | 6.1 |
| Bromocresol purple | 5.2–6.8 | Yellow | Purple | 6.3 |
| Bromothymol blue | 6.0–7.6 | Yellow | Blue | 7.1 |
| Neutral red | 6.8–8.0 | Red | Yellow | |
| Phenol red | 6.8–8.4 | Yellow | Red | 7.8 |
| Cresol red | 7.2–8.8 | Yellow | Red | 8.2 |
| Thymol blue | 8.0–9.6 | Yellow | Blue | 8.9 |
| Phenolphthalein | 8.3–10.0 | Colorless | Red | 9.6 |
| Thymolphthalein | 9.4–10.5 | Colorless | Blue | 9.9 |

occurs are given. If the pH is known when equivalent amounts of acid and base have reacted, it is usually possible to select a suitable indicator for denoting the end point in an acid-base titration. The strength of the titrant is an important factor which will determine whether the end point will be satisfactory. If the titrant is stronger than 0.1 *N*, 1 drop will cause a large change in pH and give a sharp end point. Titrants much weaker than this will not give a sharp end point, because 1 drop of the titrant will cause too small a change in pH at the end point. In selecting the proper indicator for a titration, the pH range of the indicator must clearly include the pH at the stoichiometric point of the titration, or the pH of the salt solution resulting from the acid-base titration.

In certain titrations it may be necessary to contend with a gradual color change at the end point. In such situations one should titrate to a definite color tint rather than a sharp color change. This is best effected by comparing the end-point color with that of a standard which is prepared by adjusting a solution, having the same composition as that being titrated, to the pH corresponding to the stoichiometric point. Indicator is added and all samples are titrated to a color matching that of the standard.

It is frequently possible to obtain a sharper and more distinct end point by using a *mixed indicator*. This consists of a mixture of two indicators or an indicator and an inert dye. An example is a solution containing 0.1 g of methyl orange and 0.25 g of indigo carmine in 100 ml of water. At pH 4.0 this indicator mixture produces a gray color, whereas above pH 4.0 the color is green and below the color is violet. Another example is a solution containing 70 mg of methylene green and 30 mg of phenolphthalein in 100 ml of solution. At pH 8.8 this indicator gives a light blue color; below this pH the color is green and above it the color changes to violet. Mixed indicators are of value in the titration of weak acids or bases or in displacement reactions involving salts. In these titrations the rate of change of pH near the equivalence point is less pronounced than in the titration of strong acids and bases. A mixed indicator can often be selected which will produce a narrow transition range at the desired pH value.

The concentration of the indicator solution usually ranges between 0.05 and 0.1%. Phenolphthalein indicator solution is usually a 1% solution in alcohol. From 1 to 3 drops of indicator solution are required for each 50 ml of solution being titrated for the best end-point detection.

## 5.5 TITRATION CURVES

To use indicators intelligently, it is necessary to understand how the pH changes during the course of a titration. Titration curves are developed by plotting pH values as the ordinate versus the volume of titrant added to the solution of acid or base being analyzed as the abscissa. Such curves may be constructed by determining the pH potentiometrically after an increment of titrant has been added, or the pH values may be calculated by means of the mass law equation from a knowledge of the composition of the solution after a specific volume of titrant has been added. Typical titration curves are shown in Fig. 5.1 for a strong acid, a dilute solution of a strong acid, a weak acid, and a very weak acid, all titrated with sodium hydroxide solution.

In acid-base titrations the end point occurs where there is the greatest change in pH per unit volume of titrant added. This occurs in the section of the curve which is most nearly vertical. The midpoint of this section represents the stoichiometric point of the reaction and is often referred to as the *inflection point* of the curve. In the titration of a *strong acid* with a *strong base*, a curve similar to *C* of Fig. 5.1 is obtained. This represents a titration curve for the titration of 25 ml of 0.1 *N* HCl with 0.1 *N* NaOH. The progressive addition of base will cause a decrease in the amount of hydrogen ion remaining in solution. With each addition of hydroxide ion more hydrogen ion will be neutralized forming slightly ionized water molecules. In the initial phases of the titration the increase in pH is slight since higher concentrations of hydrogen ion are present and require larger amounts of base per unit change in pH.

(It should be remembered that pH is an exponential function and not linear.) Theoretically, the end point in this titration should correspond to a pH of 7, which would be the pH of a solution containing only sodium chloride, the end product in the reaction between equivalent amounts of HCl and NaOH. However, according to the titration curve, the reaction is essentially complete at all pH values between 4.3 and 9.8. A negligible volume of base is consumed over this change in the pH of the solution. Beyond the end point the solution contains an excess of base, and as far as change in pH is concerned

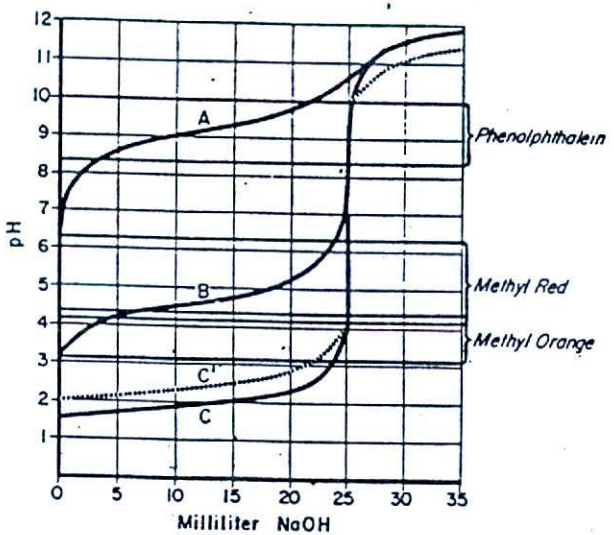



FIGURE 5.1: Typical titration curves for acids of different strength: A, 25 ml of 0.1 *N* $H_3BO_3$ with 0.1 *N* NaOH; *B*, 25 ml of 0.1 *N* $CH_3COOH$ with 0.1 *N* NaOH; *C*, 25 ml of 0.1 *N* HCl with 0.1 *N* NaOH; *C'*, 25 ml of 0.05 *N* HCl with 0.05 *N* NaOH.

the situation is similar to that in the early phases of the titration. Larger volumes of base must be added for each unit change in pH. In other words, the titration curve tends to become level when excess base is present, just as in the initial stages where excess acid is present. This curve is typical for the titration of strong acids with strong bases. When a *strong base* is titrated with a *strong acid*, the mirror image of this curve is obtained. In such titrations any indicator may be employed whose transition in colors falls on the vertical portion of the titration curve (pH 4.3 to 9.8). Any of the three indicators shown in Fig. 5.1 or any indicator listed in Table 5.1 whose color transition falls on the vertical section of the curve may be employed.

The nature of the titration curve, as mentioned earlier, depends on the strength of the titrant and on the strength of the solution being titrated. The weaker the solution, the smaller the vertical change at the end point, and

the selection of a suitable indicator becomes more important. If 25 ml of 0.05 *N* HCl is titrated with 0.05 *N* NaOH, a curve similar to *C'*, Fig. 5.1, is obtained. It is apparent that methyl orange would not be a suitable indicator for such a titration.

If phenolphthalein were used as the indicator in the titration of 25 ml of 0.1 *N* HCl with 0.1 *N* NaOH, the end point would appear when about 25.04 ml of base has been added or when the solution is but very slightly alkaline. If methyl orange were used as the indicator, the end point would come when about 24.95 ml of base has been added or when the solution is very slightly acid. The difference in using the two indicators would amount to about 0.1 ml of base. In the standardization of a solution of HCl, one would obtain two values for the normality. Although the difference would not be large, either could be considered correct. To minimize any error in this regard, the same indicator should be used for subsequent analyses as was used in the standardization. Another alternative is to conduct an *indicator blank* which would correct for the difference between the end point and the stoichiometric point. That amount of titrant is determined which is required to produce the proper color change in a solution that does not contain the desired constituent. This volume, the indicator blank, is subtracted from the volume consumed in the actual analysis. In very accurate work this titration error must be taken into account.

The titration of a *weak acid* with a *strong base* is illustrated by curve *B* in Fig. 5.1. Since acetic acid is a weak acid, it is incompletely dissociated. Therefore, the pH at the start of the titration is higher than that of hydrochloric acid. As the titration proceeds, sodium acetate is formed which will establish a buffer system, the combination of a weak acid and the salt of weak acid. In the early stages of the titration, for about the first 10% of the titration, there is an initial rapid rise in pH. The completely dissociated sodium acetate serves to decrease the hydrogen ion concentration because acetate ion represses the ionization of unreacted acetic acid. When the acetate ion concentration becomes appreciable, the solution resists changes in pH upon further addition of base (or acid), and the titration curve becomes level. Additional base forms more acetate ion which does not alter the pH of the solution. Buffer capacity reaches a maximum when the acetic acid and sodium acetate are in equal concentration or when the acetic acid is half neutralized. As the titration approaches the equivalence point, the buffer capacity is exceeded and the pH rises. At the stoichiometric point, the pH of the solution is the same as that of a solution containing only sodium acetate. Since this is a salt of a weak acid and strong base, hydrolysis occurs, producing a slightly ionized acid and a highly ionized base. The solution is therefore alkaline, and an indicator must be selected which changes color in the alkaline range. When excess base has been added to the solution, the alkalinity is due solely to the hydroxide ion, and the titration curve corresponds to that for HCl (Fig. 5.1, curve *C*) when excess base has been added.

Since the vertical segment of the titration curve at the end point is less than that observed for strong acids, one is restricted in the selection of a suitable indicator. The pH range is confined to the region 7.5 to 10. Thus, phenolphthalein becomes the indicator of choice. If methyl orange were to be used, the end point would appear when less than 10 ml of base solution was added. Since this indicator changes from red to yellow at pH 4.4, this would give a color change during the early stages of the titration corresponding to the buffer range in the titration curve. Even methyl red would be unsuitable. The end point appears about 2 ml before the equivalence point is reached, as shown in Fig. 5.1.

In considering the titration of a *weak base* by a *strong acid*, for example, ammonium hydroxide with hydrochloric acid, the situation would be similar to that described for the titration of a weak acid. The pH at the start of the titration would be about 11, and as the titration proceeds there would be an immediate drop followed by a leveling off resulting from the formation of a buffer system ($NH_4OH$-$NH_4Cl$), which would resist changes in pH upon further addition of acid. At the equivalence point the salt hydrolyzes, producing a slightly ionized base and a completely ionized acid. The solution at the equivalence point is therefore acidic. Phenolphthalein is not suitable since it would signal the end point long before the equivalence point is reached. Methyl red is commonly used for such a titration.

The titration of a *very weak acid* with a *strong base* is illustrated by curve *A* of Fig. 5.1, in which boric acid is titrated with 0.1 *N* sodium hydroxide. Boric acid, $H_3BO_3$, has an ionization constant of $5.5 \times 10^{-10}$, and it behaves as a monoprotic acid. The titration of acids whose ionization constant is less than $10^{-6}$ is not feasible with 0.1 *N* base. A sharp inflection is not obtained, and even the most suitable indicator will not produce a satisfactory color change at the equivalence point. However, in the presence of glycerol, boric acid forms a complex acid which is stronger than boric acid itself, and a satisfactory end point is produced in the phenolphthalein range.

The titration of *weak acids* with *weak bases* is of little practical value, since there is no sharp inflection at the equivalence point and there are no indicators which will produce a sharp color change at the end point. Such titrations may be effected potentiometrically or by nonaqueous titration in the proper solvent system and with a suitable titrant. These are discussed elsewhere in this text.

The titration curve for polyprotic acids (and polyhydroxy bases) will show more than one inflection point if the ionization constants for the different stages of ionization differ by a factor greater than $10^4$. Sulfuric acid, a strong diprotic acid, shows only one inflection point, since the ionization constants for the two steps in the ionization are close to one another. Phosphoric acid, on the other hand, shows two distinct inflection points. The first occurs at pH 4 and is readily detectable in a visual titration with methyl orange as the indicator. The second end point occurs at about pH 9 and is

detectable with phenolphthalein as the indicator. The third ionization constant is about $10^{-13}$ which is too near $K_w$ and does not produce a distinct inflection in the titration curve to be useful for end-point detection. A titration curve for phosphoric acid with sodium hydroxide is shown in Fig. 5.2. Mixtures of weak and strong acids, or weak and strong bases, will yield satisfactory differentiating titration curves provided the ionization

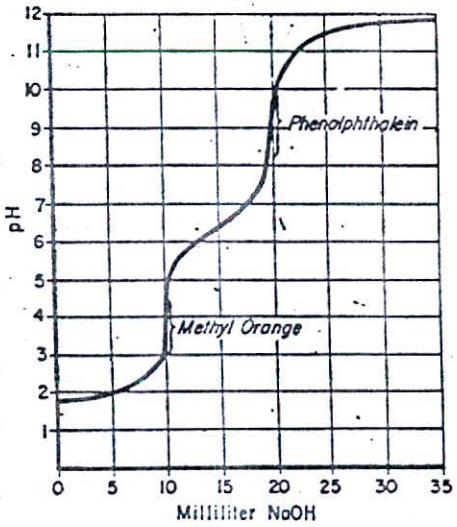



FIGURE 5.2: Titration curve for $H_3PO_4$ with 0.1 *N* NaOH.

constants for the components vary by at least $10^4$. When suitable indicators are not available for end-point detection, a potentiometric titration will generally prove useful.

## 5.6 GENERAL METHODS OF ANALYSIS

The specific titrimetric procedure employed in a particular assay depends primarily on the nature of the substance being analyzed. *Visual titrations* are employed when a suitable indicator is available to denote the end point in the titration. The solution of the sample being analyzed must not be colored or turbid, since these will obscure the end point. It is also important that the end point and stoichiometric point be identical. When a visual titration is not feasible, a *potentiometric titration* may prove useful in determining the end point in a titration. This technique depends upon the change in potential difference which occurs between two dissimilar electrodes during the neutralization reaction. The electrodes commonly employed are the calomel and

glass electrode system. In conducting a potentiometric titration, voltage readings or pH values are recorded after each increment of titrant is added to the solution being titrated. The end point in the titration occurs when there is the greatest relative change in potential upon addition of titrant. The end point is determined by plotting milliliters of titrant as the abscissa against millivolts or pH readings as the ordinate. The titration curve so obtained shows a marked change in slope or an inflection at the end point similar to the curves shown in Figs. 5.1 and 5.2. The exact end point is taken as the midpoint in the vertical portion of the curve, which actually represents the maximum change in voltage or pH per unit change of volume. Any commercially available pH meter can be used for a potentiometric titration.

A *direct titration* involves the addition of standard solution from a burette into the solution being analyzed until the end point is reached. Such a procedure is feasible when the acid or base being determined has an ionization constant of $10^{-5}$ or greater. The end point is readily discernible by the change in color of the indicator or from the inflection in the curve obtained by a potentiometric titration.

A *residual titration* or *back titration* may prove successful where direct titration fails. In this procedure a known excess of acid or base titrant, more than is sufficient to react completely with the compound being analyzed, is added to the sample. After reaction is complete, the excess reagent is determined by titration with a standard solution of the opposite species. The actual amount of reagent reacting with the desired constituent is calculated by substracting the volume consumed in the back titration from the volume added initially, after both volumes have been converted to a common normality, or a suitable correction has been made to take into account any difference in strength between the standard acid and base solutions used in the analysis.

In general, residual titrations are employed where the compound for analysis is insoluble in water, where the rate of the neutralization reaction is relatively slow, or where a volatile substance is involved which might otherwise be lost during the titration. Typical examples of analyses involving back titration include magnesia magma, zinc oxide, acetylsalicylic acid, and methenamine.

Very weak acids and very weak bases cannot be determined by direct titration, but their salts are titratable by *displacement titration* in which the very weak acid or base is displaced from its salt combination by a strong acid or base. Examples of compounds analyzed by displacement titration include sodium borate, sodium carbonate, and sodium salicylate.

In a *differentiating titration* two or more end points are produced. Such a titration may involve a mixture of a strong and weak base, a mixture of a strong and weak acid, or a polyfunctional acid or base. Indicators are frequently available for the detection of the end points. An example of this is the USP assay for sodium hydroxide in which total alkali and sodium carbonate content are determined. Phosphoric acid may be titrated differentially for

two end points, using the indicator method. In most instances a potentiometric titration is necessary for a successful differentiating titration.

For many substances, and in particular pharmaceutical agents, a special treatment is required to convert the compound into one which is titratable as an acid or base. This may involve oxidation, hydrolysis, saponification, distillation, ignition, etc. In the following section typical assay procedures are described, illustrating the general procedures noted in this section. In addition, modifications of the general procedures are indicated.

## 5.7 ACIDIMETRIC AND ALKALIMETRIC ASSAY PROCEDURES

This review is based on the assay procedures described in the *United States Pharmacopeia* and the *National Formulary*, which are referred to as official methods. Frequent reference is made to assay methods of the *British Pharmacopoeia* and procedures reported in the recent literature.

### A. DIRECT TITRATION OF ACIDIC SUBSTANCES

The general procedure involves the direct titration of the acidic substance in aqueous, hydroalcoholic, or other suitable solvent with a standard solution of sodium hydroxide as the titrant. Acidic substances titrated in this way include inorganic acids, organic carboxylic acids, certain phenolic compounds, imides, acid salts, and others. Titration is effected visually using a suitable indicator or, as in several instances, potentiometrically. For the inorganic acids, any indicator whose color transition range falls between pH 4 and 10 is suitable, since at the equivalence point a salt is formed which is not hydrolyzed in aqueous solution. Methyl red, methyl orange, and phenolphthalein are commonly employed. For organic acids phenolphthalein is most frequently used, although others are specified, depending on the pH of the solution at the equivalence point of the titration.

The concentrated inorganic acids such as hydrochloric acid are assayed by titrating a weighed sample (since the concentration is expressed as weight in weight) with 1 *N* NaOH, using methyl red as the indicator. The diluted acids, such as diluted hydrochloric acid, are assayed by titrating an exact volume with 1 *N* NaOH. Per cent concentration is expressed on a weight in volume basis. Phosphoric acid, as a weighed sample, and diluted phosphoric acid, as an exact volume sample, are titrated with standard sodium hydroxide using thymolphthalein as the indicator. When titrated to a thymolphthalein end point (pH 9.4 to 10.5), phosphoric acid behaves as a dibasic acid. Thus, the equivalent weight of $H_3PO_4$ is one-half the molecular weight, or 49.00.

In the analysis of carboxylic acids, titration is effected visually with 1 or 0.1 *N* NaOH, using phenolphthalein as the indicator. A typical example is

acetic acid. Acetic acid and glacial acetic acid are assayed as weighed samples, whereas for diluted acetic acid an exact volume is titrated. Benzoic acid and salicylic acid are dissolved in neutralized diluted alcohol prior to titration with 0.1 *N* NaOH. The BP employs phenol red as the indicator for salicylic acid, and in the USP bromothymol blue is the indicator for salicylic acid collodion. Bromothymol blue is also the indicator in the assay of glutamic acid hydrochloride. At this end point, two of the hydrogens are neutralized and the equivalent weight is one-half the molecular weight. Other examples of carboxylic acids titrated by this general procedure include tartaric acid, nicotinic acid, oxidized cellulose, probenecid, dehydrocholic acid, and citrated caffeine for citric acid.

Phenols are, in general, too weakly acidic in water to be titrated directly with base. However, bithionol, dissolved in acetone, and hexachlorophene, dissolved in alcohol, are sufficiently strong as acids to be titrated potentiometrically with 0.1 *N* NaOH. Tolbutamide, saccharin, and vinbarbital contain an imido hydrogen which is sufficiently acidic to be titrated with 0.1 *N* NaOH. Phenolphthalein is the indicator for the first two and thymolphthalein is the indicator for the third. The hydrochloric acid of mechlorethamine hydrochloride is titrated potentiometrically with 0.01 *N* NaOH to a predetermined pH value. Potassium bitartrate, $KHC_4H_4O_6$, and sodium biphosphate, $NaH_2PO_4$, are acid salts titrated with 1 *N* NaOH to a phenolphthalein end point. In the assay of sodium biphosphate, sodium chloride is added, and the titration is carried out in the cold to reduce hydrolysis and produce a more reliable end point. The equation for the reaction is

$$NaOH + NaH_2PO_4 = Na_2HPO_4 + H_2O$$

Since only one hydrogen is neutralized, the equivalent weight is the same as the molecular weight.

## B. DIRECT TITRATION OF BASIC SUBSTANCES

A large number of bases, both organic and inorganic, are determined by direct titration with a standard acid. The indicator used depends on the pH at the equivalence point of the titration, which will be determined by the strength of the base being titrated.

The strong bases sodium hydroxide and potassium hydroxide are analyzed for total alkali, expressed as hydroxide, and for carbonate, a usual contaminant of the hydroxide. Analysis is accomplished by a differentiating titration or a double titration. A weighed sample of the alkali is dissolved in water and titrated with 1 *N* sulfuric acid to a phenolphthalein end point. At the discharge of the pink color, methyl orange indicator is added and the titration is continued to a second end point or to the appearance of a permanent pink color. A potentiometric titration curve would show two inflections.

The first end point represents the volume of acid required to neutralize completely the hydroxide in the sample and the volume needed to convert the

carbonate to the bicarbonate. The equations for the reactions may be represented as follows:

$$2NaOH + H_2SO_4 = Na_2SO_4 + 2H_2O$$
$$2Na_2CO_3 + H_2SO_4 = Na_2SO_4 + 2NaHCO_3$$

The first end point (phenolphthalein), corresponding to the first break in the titration curve, occurs at about pH 8.4, which is in the range where the indicator changes from pink to colorless. This represents a solution containing sodium bicarbonate, the only end product of the titration affecting the pH. If at the discharge of the pink color, methyl orange is added, the color of the solution will be orange. The second titration is continued to a methyl orange end point or to the appearance of a persistent pink color. In this titration the sodium bicarbonate is converted to carbon dioxide and water according to the equation

$$2NaHCO_3 + H_2SO_4 = H_2O + CO_2 + Na_2SO_4$$

The second end point occurs at the pH of about 4.2, which is within the range where methyl orange undergoes its color change.

From the volumes of acid consumed in the first and second end points, one can readily calculate the carbonate and total alkali concentrations. Although a part of the volume of acid consumed was used in converting the carbonate to $CO_2$ and $H_2O$, the USP specifications are for *total alkali* expressed as sodium hydroxide. Therefore, each milliliter of 1 *N* acid consumed represents 40 mg of sodium hydroxide (1 meq). The total alkali in the sample, as hydroxide and carbonate, is obtained by multiplying the total volume of acid consumed by 40, the milliequivalent weight of sodium hydroxide in milligrams. The volume consumed in the second titration (from the phenolphthalein end point to the methyl orange end point) is involved only in the conversion of the sodium bicarbonate to $CO_2$ and $H_2O$, and a similar volume as part of the first titration is involved in the conversion of the sodium carbonate to sodium bicarbonate. The USP also gives specifications for sodium carbonate. This may be readily calculated from the volume of acid consumed in the second titration. Since this represents a displacement reaction involving 1 equiv for each mole of sodium carbonate (the other equivalent being consumed in the first titration), the equivalent weight then is the same as the molecular weight of $Na_2CO_3$ or 106.0. Alternatively, the total volume of acid consumed in the conversion of the carbonate to $CO_2$ and $H_2O$, or double the volume used for the second end point, may be used to calculate the carbonate content. Since 2 equiv are now involved for each mole of sodium carbonate, the equivalent weight must be taken as 53.0. It is apparent that by either scheme, the carbonate value will be the same. In the first method, the equivalent weight is double that in the second method, but the volume used is half that used in the second method. The student should understand the logic in both methods of calculation.

The following problem illustrates the calculations involved in a typical assay.

EXAMPLE 11: A sample of sodium hydroxide weighing 1.250 g is assayed by titration with 1 *N* sulfuric acid. Titration to the phenolphthalein end point required 29.30 ml of the acid, and an additional 0.42 ml of acid was required for the methyl orange end point. Calculate the per cent total alkali and the per cent sodium carbonate in the sample taken for analysis.

*Solution:* Since the total volume of 1 *N* $H_2SO_4$ consumed in assay is 29.30 + 0.42 or 29.72 ml, the total alkali calculated as NaOH is

$$\frac{29.72 \times 40.00 \times 100}{1250} = 95.10\%$$

The amount of $Na_2CO_3$ present is

$$\frac{0.42 \times 106.0 \times 100}{1250} = 3.56\%$$

In the official assay for potassium hydroxide, the procedure is the same as that described for sodium hydroxide, except that the specifications are in terms of total alkali, calculated as KOH, and carbonate in terms of $K_2CO_3$.

The BP assay for sodium hydroxide is also in terms of total alkali and sodium carbonate. The assay procedure, however, is slightly different from the USP method. Barium chloride solution is added to a solution of the alkali to precipitate the carbonate as barium carbonate. The solution is then titrated with 1 *N* HCl to a phenolphthalein end point. The solution is titrated slowly with constant shaking to prevent the acid from reacting with the insoluble carbonate. The volume of titrant consumed in the first end point represents the neutralization of only the sodium hydroxide. The carbonate will not react so long as the solution is alkaline. Bromophenol blue indicator is added, and the titration is continued to the first permanent green color which persists upon shaking the solution. At the second end point the carbonate has been converted to $CO_2$ and $H_2O$.

The actual amount of sodium hydroxide in the sample analyzed by the official procedure can be readily calculated from the data obtained in the titration. As indicated earlier, the same volume of acid consumed in the conversion of the sodium bicarbonate to carbon dioxide and water (methyl orange end point) was also consumed in the titration to the first end point. Therefore, subtracting the volume consumed in the second end-point titration from the volume consumed in the first end point gives the volume used in the neutralization of the sodium hydroxide.

The official assay procedure for sodium hydroxide can also be modified for the determination of mixtures of sodium carbonate and sodium bicarbonate.

The assay for aromatic ammonia spirit for the content of ammonium

in the assay of sodium hydroxide for sodium carbonate. The ammonium salt is converted to sodium carbonate by adding standard sodium hydroxide and heating until all ammonia has been expelled. The solution is then titrated with standard sulfuric acid to a phenolphthalein end point. This neutralizes excess sodium hydroxide and converts the sodium carbonate to sodium bicarbonate, a 1-equiv change. Titration is continued to a methyl orange end point. The volume of standard acid consumed in the second end point is used for calculation of the carbonate content of the spirit.

Calcium hydroxide solution, a rather strong base, is titrated with standard hydrochloric acid to a phenolphthalein end point. Since the carbonate content is not required, the titration is not continued to a methyl orange end point. The official assay procedure for calcium hydroxide, slaked lime, is not alkalimetric, whereas the BP method is based on titration with standard HCl. Since the assay is for $Ca(OH)_2$ content only, interference resulting from $CaCO_3$, which is readily formed by absorption of $CO_2$ from the atmosphere, is miminized by its insolubility in sucrose solution. Strong and diluted ammonia solutions are titrated with standard $H_2SO_4$ to a methyl red end point. This represents a typical titration of a weak base with a strong acid. In a similar manner ethylenediamine solution, aminophylline for ethylenediamine content, and mono- and triethanolamine are titrated with standard hydrochloric acid using indicators whose color transitions occur in the acid pH range.

Where an acid is too weak for direct titration with standard base, the alkali salt can usually be assayed by direct alkalimetry by a displacement reaction. The strong acid titrant displaces the weak acid from its salt combination. Sodium and potassium carbonate, the bicarbonates, and sodium borate are typical examples. The indicator is usually methyl orange or methyl red. In the assay of sodium borate the equation for the reaction is

$$Na_2B_4O_7 \cdot 10H_2O + 2HCl = 4H_3BO_3 + 2NaCl + 5H_2O$$

Methyl red is a suitable indicator, since it is not affected by the very weak acid, $H_3BO_3$, but does show a color change in the presence of HCl at the end point. In the BP assay procedure for sodium phosphate, $Na_2HPO_4$, a mixed indicator consisting of bromocresol green and methyl red is employed. It is titrated with standard HCl to an end point corresponding to pH 4.4, and the equation for the reaction is

$$Na_2HPO_4 + HCl = NaH_2PO_4 + NaCl$$

It is apparent from the equation that the equivalent weight for sodium phosphate in this assay is the same as the molecular weight.

## C. RESIDUAL TITRATION OF ACIDIC AND BASIC SUBSTANCES

Lactic acid is an example of an acidic substance determined by residual titration. Since this actually represents a mixture of lactic acid and lactic anhydride, reaction with base is too slow for a direct titration. Therefore,

a measured excess of base titrant is added, the solution is heated, and the excess base is titrated with standard acid with phenolphthalein as indicator.

A number of basic substances are titrated residually for the reasons mentioned earlier. Zinc oxide is insoluble and reacts slowly with sulfuric acid. In the official assay a sample of the oxide is dissolved in a measured excess of standard sulfuric acid with the aid of gentle heat. When solution is complete, the excess acid is determined by titration with standard base. Ammonium chloride is added to prevent precipitation of $Zn(OH)_2$ during the titration. Zinc undecylenate is dissolved in standard sulfuric acid solution, and the displaced undecylenic acid is extracted with solvent hexane. The excess acid is determined by residual titration with standard base. Calamine is also determined by residual titration. Methyl orange is the usual indicator for such titrations.

Several insoluble magnesium preparations are analyzed by residual titration. These include magnesia magma, magnesium carbonate, the oxide, the stearate, and the trisilicate. In each instance an excess of standard $H_2SO_4$ is added and after solution is effected, the excess acid is titrated with standard base. Methyl orange is used as the indicator except for the magma, for which methyl red is employed. In the BP assay for magnesia magma, methyl orange is the indicator. In the assays for magnesium carbonate and magnesium oxide, a correction must be made for the presence of calcium oxide, a contaminant in the official preparations.

The sodium bicarbonate content of sodium bicarbonate and calcium carbonate powder and tablets, and sodium bicarbonate and magnesium oxide powder and tablets is determined by adding an excess of standard HCl, heating, and titrating the excess acid with standard base. A correction is made for the calcium carbonate or magnesium oxide, the other component in these dosage forms. The sodium bicarbonate content of compound effervescent powders is determined similarly.

The assay for total ammonia in aromatic ammonia spirit and in ammonium carbonate is a residual alkalimetric titration procedure. Also, the BP assay for strong ammonia solution is a residual titration. Since $NH_3$ is a volatile substance, residual titration is used to minimize loss during the titration process.

The free bases lidocaine and ephedrine are determined by residual alkalimetry. In the assay for lidocaine, a mixed indicator consisting of bromocresol blue and methyl red is used for end-point detection. In the ephedrine assay, methyl red is the indicator.

The assay procedures discussed in this and the previous classes include those which involve little or no pretreatment of the constituent being analyzed. In subsequent categories the procedures described may involve direct or residual titration, but the classification is based on some special treatment prior to the actual titration process. Importance is attached to the special technique or unusual treatment rather than whether the assay is direct or

residual. It should also be recognized that some assay procedures could, with equal justification, be classified into more than one category.

## D. DETERMINATION OF ACID LIBERATED FROM SALT OR ESTER COMBINATION

In this category are included salts and esters which are analyzed by titrating the acid released by hydrolysis, by addition of a strong acid, or by saponification with standard alkali solution, aqueous or alcoholic. Direct or residual titration of the acid may be involved. Also included in this group are hydroxyl-containing compounds which are first esterified with acetic anhydride and subsequently saponified with standard base.

In the assay for sodium salicylate, an aqueous solution of a weighed sample is in contact with an ether layer in a separator. The aqueous layer is titrated with standard HCl to a pale green end point with bromophenol blue indicator. As HCl is added to the aqueous layer, salicylic acid is liberated and is extracted into the ether layer. At the equivalence point only sodium chloride is present in the aqueous layer, and the first drop of acid then produces the indicator color change. In sodium salicylate injection, the salicylic acid is liberated with diluted hydrochloric acid and extracted with ether. After evaporation of the ether, the salicylic acid is titrated in a hydroalcoholic solution to a phenolphthalein end point with standard NaOH. In the analysis of the ester phenyl salicylate in the tablet dosage form, the phenyl salicylate is hydrolyzed with base to form phenol and sodium salicylate. The solution is acidified with HCl, and the salicylic acid is extracted in a separator with ether. The ether is evaporated and the salicylic acid in a water-alcohol solution is titrated with standard base as mentioned for sodium salicylate injection. In the assay of the combination theobromine sodium salicylate for sodium salicylate, after precipitation of the theobromine, the solution is acidified and the salicylic acid is extracted with chloroform. Most of the chloroform is removed by evaporation, alcohol is added, and the salicylic acid is determined with standard base.

The assay for sodium benzoate is similar to that for sodium salicylate, except that methyl orange is used as the indicator, and titration with acid is continued until a permanent orange color is produced in the water layer.

Saccharin calcium and saccharin sodium are treated with diluted hydrochloric acid and the precipitated saccharin is extracted with chloroform-alcohol (9 to 1) solvent. After evaporation of the solvent, the saccharin is titrated with standard base to a phenolphthalein end point. Sodium dehydrocholate injection is treated in essentially the same manner. Thymol blue is the indicator and chloroform is the extracting solvent.

Esters, in general, are assayed by a saponification procedure involving the use of standard alcoholic KOH or standard aqueous NaOH. By this technique, the sample is heated with a measured excess of base and the excess

titrated with standard acid. A blank is usually conducted in the same manner except the desired constituent is not present. The difference between the volume consumed in the blank and the volume consumed in the titration with the desired constituent present represents the actual volume of standard base equivalent to substance being assayed. This corrected volume is used in calculating the quantity of desired constituent in the sample for analysis.

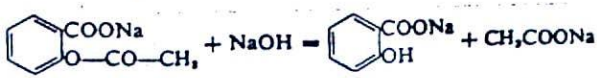
Ethyl acetate is a typical ester analyzed by this procedure. The sample is saponified under reflux with standard NaOH for 1 hr. The excess NaOH is titrated with standard HCl to a phenolphthalein end point. A blank run is conducted. The equation for the reaction is

$$CH_3COOC_2H_5 + NaOH = CH_3COONa + C_2H_5OH$$

The ethyl acetate content is equivalent to the actual volume of base consumed in the reaction. The equivalent weight of the ethyl acetate will be the same as the molecular weight, since the reaction is mole for mole. Methylparaben and propylparaben are assayed similarly, except that the excess base is titrated to a pH 6.5 end point with bromothymol blue as the indicator.

Alcoholic potassium hydroxide is frequently employed in the determination of esters. The alcohol serves as a mutual solvent. Typical esters or ester-containing preparations analyzed in this way include methyl salicylate, benzyl benzoate, peppermint oil, and rosemary oil. Alcoholic KOH is used in the determination of the saponification value and ester value of fixed oils.

Acetylsalicylic acid, which is both an organic acid and an ester, is assayed by heating with an excess of 0.5 *N* NaOH. The excess base is titrated with 0.5 *N* $H_2SO_4$ to a phenolphthalein end point. The carboxyl groups of the salicylic acid and the acetic acid, which are liberated as a result of the alkaline hydrolysis of acetylsalicylic acid, are neutralized by the base. As a result, each mole of acetylsalicylic acid reacts with 2 moles of NaOH. Since the molecular weight of acetylsalicylic acid is 180.16, each milliliter of 0.5 *N* NaOH is equivalent to 45.04 mg, which is the titer value as stated in the official compendium. For the tablets, however, the acetylsalicylic acid is extracted with neutralized alcohol and the solution, in the cold, is titrated to a phenolphthalein end point. The carboxyl group of the intact molecule is neutralized as well as any acetic acid and salicylic acid, the hydrolytic products, which may be present. The volume of standard base required for this first end point is noted and an equal volume plus 15 ml excess is added. The solution is heated to effect the saponification of the intact ester. Only the acetic acid released by the ester is neutralized by base as a result of the saponification. The equation for the reaction is



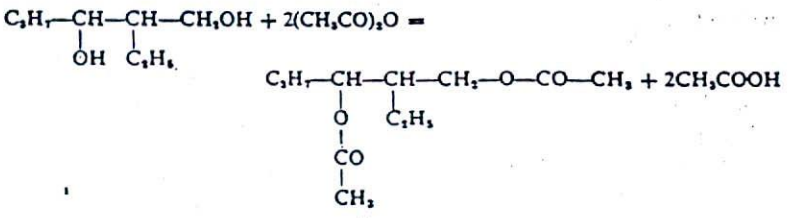

One mole of acetylsalicylic acid reacts with 1 mole of NaOH. Each milliliter of 0.1 *N* NaOH consumed in the second titration is equivalent to 18.02 mg

of acetylsalicylic acid, as indicated in the official compendium. The assay for the capsule dosage form is the same as for the tablets. It should be noted that the assay of the tablets and capsules is for unhydrolyzed acetylsalicylic acid only.

Butyl chloride is assayed by alkaline hydrolysis under reflux conditions with a measured excess of standard alcoholic potassium hydroxide. The excess base is titrated with standard hydrochloric acid. Busulfan, a methanesulfonic acid ester of tetramethylene glycol, is analyzed by titrating the methanesulfonic acid released when the compound is heated under reflux in the presence of water. The titrant is 0.05 *N* sodium hydroxide. Since each molecule of busulfan releases two molecules of methanesulfonic acid, the equivalent weight is one-half the molecular weight (246.31), or each milliliter of 0.05 *N* sodium hydroxide is equivalent to 6.158 mg of busulfan.

In the assay of peppermint oil for total menthol and in the assay of rosemary oil for total borneol, the free alcohols are transformed into their corresponding acetates by esterification with acetic anhydride in the presence of sodium acetate. Excess acetic anhydride is removed, and the acetylated oil is dried over anhydrous sodium sulfate. The ester in the oil is then saponified with standard alcoholic KOH according to the residual titration procedure described earlier for the determination of the ester content of these oils. The total alcohol present in the original sample is calculated by the method described in the official compendium. A correction is made for acetylated alcohol present in the original sample.

Ethohexadiol is assayed by acetylation of the two hydroxyl groups by heating with acetic anhydride in the presence of pyridine which produces the corresponding acetate. Each hydroxyl group in the molecule reacts with a molecule of acetic anhydride to produce one molecule of acetic acid. The equation for the reaction is



The acetic acid released as a result of the reaction and acetic acid resulting from the decomposition of excess acetic anhydride are titrated with standard alcoholic KOH. A mixed indicator, consisting of cresol red and thymol blue, is used in the titration. A blank determination is conducted. The content of ethohexadiol is calculated from the volume of alcoholic KOH equivalent to the acetic anhydride actually consumed in the acetylation of the hydroxyl groups. Since each molecule of ethohexadiol (mol. wt. 146.23) releases two

molecules of acetic acid from two molecules of acetic anhydride, the equivalent weight is one-half the molecular weight, and each milliliter of 0.5 *N* alcoholic KOH consumed is equivalent to 36.56 mg of ethohexadiol. The pyridine does not interfere in the titration, since it is too weakly basic. Benzyl alcohol, BP, and dienoestrol, BP, are analyzed by a similar technique. The same general procedure is used for determining the hydroxyl number in such compounds as stearyl alcohol and cetyl alcohol. Acetyl chloride in toluene is the acetylating agent, and pyridine is a condensing agent for the reaction.

## E. RESIDUAL ALKALIMETRY FOLLOWING SOLVENT EXTRACTION

Most salts representing a combination of an organic base and a mineral acid are analyzed by basifying an aqueous solution of the salt with ammonium hydroxide, sodium hydroxide, or sodium carbonate. The stronger inorganic base displaces the weak organic base from its salt form. The free base is then extracted with an organic solvent, usually chloroform or ether. This is accomplished by means of a separatory funnel or a continuous-extraction apparatus. Frequently, the aqueous phase is saturated with sodium chloride to effect a more efficient separation of the base. After removal of the solvent, the free base is treated with an excess of standard acid and the unreacted acid is titrated with standard base. In some procedures the standard acid is added prior to the complete removal of the organic solvent. The excess solvent is driven off prior to the titration of the excess acid. The indicator is usually methyl red. Most alkaloid salts are assayed in this way. Typical examples are morphine sulfate, codeine phosphate, ephedrine hydrochloride, and scopolamine hydrobromide. Many salts of synthetic bases are also determined in this manner. These include amphetamine sulfate, methadone hydrochloride, piperocaine hydrochloride, and procaine hydrochloride dosage forms.

The assay for amphetamine sulfate illustrates the general procedure. A weighed sample is dissolved in water and added to a separator. The solution is rendered alkaline with sodium hydroxide solution and extracted with six 15-ml portions of ether. An excess of standard sulfuric acid is added to the ether extract, and the ether is expelled with gentle heat. The excess acid is titrated with standard sodium hydroxide, using methyl red as the indicator. The equations for the reactions involved in this assay are

$$(C_9H_{13}N)_2H_2SO_4 + 2NaOH = 2C_9H_{13}N + 2H_2O + Na_2SO_4$$

$$2C_9H_{13}N + H_2SO_4 = (C_9H_{13}N)_2H_2SO_4$$

$$H_2SO_4 + 2NaOH = Na_2SO_4 + 2H_2O$$

Since each mole of sulfuric acid is equivalent to 1 mole of amphetamine sulfate, the equivalent weight of the latter is one-half its molecular weight (368.50). Each milliliter of 0.1 *N* sulfuric acid is equivalent to 18.42 mg of $(C_9H_{13}N)_2H_2SO_4$.

The general procedure for salts of organic bases is usually applicable to the dosage forms containing the salt, although modifications may be required where interfering substances are present.

Ion exchange resins have proved useful in isolating organic bases from their salt combination. The tedious and time-consuming solvent extraction process is thus avoided. The weak anion exchange resins (polyamine-type) and the strong anion exchangers (quaternary ammonium base-type) are used for removing the acid portion of the salt. The organic base passes into the eluate and is determined by direct or residual titration. Although not employed in the official assay procedures of the USP or NF, their application to the analysis of salts of organic bases is of interest. Jindra[3–5] used the weak anion exchange resin Amberlite IR-4B for the analysis of alkaloidal salts. The salt dissolved in a hydroalcoholic solvent is passed through the column. The free base is eluted from the column with an aqueous-alcoholic solvent, and the eluate is titrated with standard hydrochloric acid. Saunders et al.[6] used a strong anion exchange resin for the determination of alkaloidal salts. Inorganic salts interfere, since the quaternary ammonium base type resins are salt splitters. All metal cations appear as the hydroxide in the eluate together with the alkaloid base and are titrated by the hydrochloric acid. The strong anion exchangers are more effective in cleaving alkaloidal salts than the weak anion exchangers. Blaug and Zopf[7] used Amberlite IR-4B and Amberlite IRA-410, a strong anion exchanger, for the determination of ten antihistamine salts of varied structural types. The salt, dissolved in 60% ethanol, was passed through the resin column. The free base, eluted from the column with the same solvent, was titrated with 0.1 *N* hydrochloric acid, using bromocresol green as the indicator. Vincent et al.[8] analyzed a variety of sympathomimetic amine salts, as such and in different dosage forms. Both strong and weak anion exchange resins were employed in separating the acid fragment from the base portion of the salt. The eluent was 75% ethanol. Titration was effected visually with 0.1 *N* hydrochloric acid using methyl red as the indicator. Direct and residual titrations were employed. A number of local anesthetic salts were analyzed by Jindra and Rentz[9] through the use of Amberlite IRA-400, a strong anion exchanger. The eluent was ethanol and the eluate was titrated with standard hydrochloric acid, using methyl red as the indicator.

## F. ALKALI SALTS OF ORGANIC ACIDS

When an acid is too weak to be titrated with a standard base, the alkali salt of that acid is usually titratable with standard acid. Sodium borate and sodium carbonate are examples already noted. When an acid is weak but titratable by strong base, the titration of the alkali salt is usually not feasible. Most alkali salts of organic acids cannot be determined by a displacement reaction titration with a strong acid because the liberated acid is not weak

enough to permit the reaction to go to completion. In the assays for sodium benzoate and sodium salicylate, the reaction is quantitative because the liberated organic acid is removed with an immiscible solvent. Sodium morrhuate injection is assayed by adding a measured excess of standard sulfuric acid. The displaced organic acid, morrhuic acid, is extracted with solvent hexane, and the excess sulfuric acid is determined with standard base using methyl orange as indicator. The usual procedure for assaying alkali salts of organic acids is to convert them to the corresponding carbonate which is titratable with standard acid solution. The salt is carefully ignited in a crucible until thoroughly carbonized. Sodium acetate, as an illustration, undergoes the following reaction when it is carbonized:

$$2CH_3COONa + 4O_2 = Na_2CO_3 + 3H_2O + 3CO_2$$

The carbonized mass is treated with a measured excess of standard sulfuric acid. The reaction which is involved is shown by the equation

$$Na_2CO_3 + H_2SO_4 = Na_2SO_4 + H_2O + CO_2$$

The excess sulfuric acid is titrated with standard base using methyl orange as the indicator. From the above equations it is apparent that 2 moles of sodium acetate produce 1 mole of sodium carbonate which neutralizes 1 mole or 2 equiv. of sulfuric acid. Therefore, each milliliter of 0.5 *N* sulfuric acid is equivalent to 0.5 meq of anhydrous sodium acetate or 41.02 mg. For potassium citrate, $K_3C_6H_5O_7$, 2 moles form 3 moles of potassium carbonate upon carbonization. This neutralizes 6 equiv of sulfuric acid, and each milliliter of 0.5 *N* sulfuric acid is equivalent to $\frac{1}{6}$ meq or 51.07 mg of anhydrous potassium citrate. In general, the volume of standard acid actually consumed by the carbonized sample multiplied by the equivalence factor for the particular salt under analysis represents the amount of salt in the sample. Typical alkali salts analyzed in this way include potassium sodium tartrate, sodium propionate, sodium citrate, and potassium acetate. Liquid dosage forms such as sodium lactate injection and lactated Ringer's injection are evaporated to dryness prior to the carbonization of the sodium lactate.

Alkali salts of organic acids can be readily determined by the use of a strong cation exchange resin. Blaug[10] passed a solution of the salt through a column of Amberlite IR-120, a sulfonic acid resin. The cation of the salt was retained by the column. The organic acid appeared in the eluate and was titrated by standard base. The method was applied to liquid dosage forms.

## G. MODIFICATION OF MOLECULE PRODUCING TITRATABLE ACID OR BASE

Many compounds, as such, are not titratable with acid or base but as a result of some modification of the molecule, they are transformed into an acid or base which is titratable. In some instances an acid or base is released as a

result of the treatment and is readily titrated with a standard acid or base solution. In other cases, the compound may be too weak an acid or base to be titrated and is, therefore, converted into an acid or base which is sufficiently strong to be titrated.

Boric acid is a very weak acid with an ionization constant of $K_a = 6 \times 10^{-10}$. It is too weak an acid to be titrated visually with a standard base. The metaborate salt formed in the neutralization reaction

$$NaOH + H_3BO_3 = NaBO_3 + 2H_2O$$

is highly hydrolyzed, since it is a salt of a strong base and very weak acid, and a sharp inflection in the titration curve is not obtained. No indicator is available which will show the end point in the titration. However, in the presence of glycerol, mannitol, and many other polyhydric compounds, boric acid is apparently transformed into comparatively strong complex acids which permit the direct acidimetric titration in water with phenolphthalein as the indicator.

According to the official procedure, the sample of boric acid is dissolved in 100 ml of 50% glycerol, and the solution is titrated with standard sodium hydroxide to a phenolphthalein end point. An additional 50 ml of glycerol is added and the titration continued until the pink color reappears. Since boric acid is a monobasic acid, the equivalent weight is the same as the molecular weight, and each milliliter of 1 *N* NaOH is equivalent to 61.84 mg of $H_3BO_3$. The complex acid formed with glycerol is referred to as glycerylboric acid. The concentration of glycerol in the assay should be at least 30% of the solution to prevent the hydrolysis of the complex acid.

The ointment and solution dosage forms are assayed in the same manner. In the BP method, mannitol is used to form a complex with the boric acid. In the BP assay for borax, two titrations are conducted. The weighed sample is first titrated to a methyl red end point with standard hydrochloric acid. The volume of acid consumed is noted and the boric acid liberated in the titration is then determined in the presence of mannitol by titration with standard sodium hydroxide, using phenolphthalein as the indicator. The double titration procedure is apparently employed for the purpose of detecting the presence of sodium carbonate or boric acid: contaminants which would affect one end point or the other, if present.

Benzaldehyde is determined by reacting a weighed sample with an excess of hydroxylamine hydrochloride. The equation for the reaction is

$$C_6H_5CHO + H_2NOH{\cdot}HCl = C_6H_5CH{=}NOH + H_2O + HCl$$

For each molecule of benzaldehyde that reacts, one molecule of benzaldoxime is formed and a molecule of hydrochloric acid is liberated. The HCl is titrated with standard sodium hydroxide to the light green end point of bromophenol blue indicator. This indicator is used because its color transition occurs on the acid side of the pH scale and permits the detection of the end point in the titration of the free hydrochloric acid. If phenolphthalein were used as the

indicator, both the free and combined HCl (as the hydroxylamine salt) would be titrated. A blank is conducted in the exact same manner as the actual run except for the desired constituent. The corrected volume of sodium hydroxide solution required to neutralize the liberated HCl is used to calculate the amount of benzaldehyde in the sample for analysis. Each milliliter of 1 *N* sodium hydroxide is equivalent to 106.1 mg of $C_7H_6O$.

Ammoniated mercury is assayed according to the BP method by treating a weighed sample with an excess of potassium iodide in water. The equation for the reaction is

$$NH_2HgCl + 2KI + 2H_2O = NH_4OH + KOH + KCl + HgI_2$$

The total alkali liberated as a result of the reaction is titrated with standard hydrochloric acid, using a mixed indicator of methyl orange and xylene cyanol FF for the end-point detection. Since each molecule of ammoniated mercury releases two molecules of base, the equivalent weight is one-half the molecular weight. Each milliliter of 0.1 *N* HCl is equivalent to 12.6 mg of $NH_2HgCl$. The ointment is assayed similarly.

Several compounds are analyzed by forming an insoluble silver salt by reaction with silver nitrate. The silver ion replaces an acidic hydrogen, which combines with the nitrate ion to form nitric acid. The liberated nitric acid is then titrated with standard base solution. Propylthiouracil and methimazole and their tablet dosage forms are assayed in this manner. The liberated nitric acid is titrated with standard sodium hydroxide to a permanent blue-green color of bromothymol blue indicator solution. Since 1 equiv of nitric acid is released for each mole of compound being analyzed, the equivalent weight is the same as the molecular weight. Ethinamate and ethchlorvynol contain an acetylenic hydrogen which reacts with silver nitrate to release a molecule of nitric acid. The nitric acid is titrated with standard sodium hydroxide using a mixed indicator of methyl red and methylene blue. The assay for theobromine combinations with calcium salicylate, sodium acetate, and sodium salicylate, and their dosage forms is based on this procedure. The indicator in these titrations is phenol red.

In the assay for methenamine, a weighed sample is treated with a measured excess of standard sulfuric acid. The solution is boiled gently until the odor of formaldehyde is no longer perceptible. In the presence of sulfuric acid, methenamine is decomposed into ammonia and formaldehyde; the ammonia combines with the sulfuric acid to form ammonium sulfate. The equation for the reaction is

$$(CH_2)_6N_4 + 6H_2O + 2H_2SO_4 = 2(NH_4)_2SO_4 + 6HCHO$$

The excess sulfuric acid is titrated with standard sodium hydroxide to a methyl red end point. Since 1 mole of methenamine reacts with 4 equiv of sulfuric acid, each milliliter of 1 *N* sulfuric acid is equivalent to 35.05 mg of methenamine.

Meprobamate is analyzed according to the official procedure by first hydrolyzing with hydrochloric acid under reflux. The carbamic acid which is released is then titrated by a formol titration. This involves the addition of formaldehyde which destroys the basic properties of the amino group by forming the methylol or dimethylol derivative and permits the titration of the carboxyl group with standard base to a phenolphthalein end point. Since two carbamic acids are released from each molecule of meprobamate, the equivalent weight is one-half the molecular weight. Aminoacetic acid and the elixir dosage form of the NF X were analyzed by the formol titration procedure. The conversion of aminoacetic acid to the methylol or dimethylol derivative increases the acidity of the aminoacetic acid permitting direct titration with standard sodium hydroxide. Aminoacetic acid was titrated potentiometrically to an equivalence point of pH 9.2. The elixir, however, was titrated visually after treatment with charcoal to a phenolphthalein end point. Both preparations are now assayed by nonaqueous titration as described in the NF XI.

Guanethidine sulfate, the normal sulfate of 1-(2-guanidinoethyl)-azacyclooctane, BP, is assayed by liberating the sulfuric acid from the salt combination by passage of a weighed sample in water solution through a column of strong acid cation exchange resin, such as Amberlite IR-120. The cation is retained by the column, while the sulfuric acid appears in the eluate, which is titrated with standard base to a methyl red end point.

Chloral hydrate is treated with a measured excess of standard sodium hydroxide solution. The excess base is titrated with standard acid to a phenolphthalein end point. In the presence of base each molecule of chloral hydrate is converted to a molecule of chloroform and a molecule of sodium formate according to the equation

$$CCl_3CH(OH)_2 + NaOH = CHCl_3 + HCOONa + H_2O$$

The chloral hydrate content in the sample for analysis is calculated from the volume of base actually consumed in the reaction. In the assay described in the BP the procedure is essentially the same, except that an additional step is conducted to correct for any chloroform which in the presence of alkali has been converted to formic acid and hydrochloric acid.

Formaldehyde solution is determined by treating a weighed sample with a measured excess of standard sodium hydroxide and neutralized hydrogen peroxide. The solution is heated on a steam bath and the excess base is titrated with standard sulfuric acid to a bromothymol blue end point. The formaldehyde is oxidized to formic acid by hydrogen peroxide and is immediately converted to the sodium salt as shown by

$$HCHO + H_2O_2 + NaOH = HCOONa + 2H_2O$$

The equivalent weight of formaldehyde is the same as the molecular weight, and 1 ml of 1 *N* sodium hydroxide is equivalent to 30.03 mg of HCHO.

Triethylenemelamine is analyzed by titrating with standard acid the sodium hydroxide released when the ethyleneimine groups react with sodium thiosulfate. Three moles of sodium hydroxide are released from each mole of triethylenemelamine. Therefore, the equivalent weight is one-third the molecular weight.

## H. PHOSPHOMOLYBDATE ASSAY FOR PHOSPHATES

Phosphates may be determined by precipitation of the phosphate from a warm nitric acid solution of a weighed sample by addition of an excess of ammonium molybdate, $(NH_4)_2MoO_4$. Precipitation is carried out in a warm solution because of the colloidal nature of the precipitate. Since the composition of the yellow precipitate is not definite enough, gravimetric analysis is not employed. Instead, the precipitate is washed free of nitric acid on a filter and is dissolved in a measured excess of standard sodium hydroxide solution. Excess base is titrated with standard sulfuric acid to a phenolphthalein end point. The equation for the reaction is

$$(NH_4)_3PO_4 \cdot 12MoO_3 + 23NaOH = 11Na_2MoO_4 + NaNH_4HPO_4 + (NH_4)_2MoO_4 + 11H_2O$$

Potassium phosphate, $K_2HPO_4$, sodium phosphate, $Na_2HPO_4$, tribasic calcium and magnesium phosphates, and aluminum phosphate gel are analyzed by this procedure.

Assay procedures involving the Kjeldahl method and modifications of the Kjeldahl method are covered in Chapter 9.

## QUESTIONS

Q5.1. Define the following terms: equivalent weight, stoichiometric point, primary standard, secondary standard, acid, differentiating titration, normality, molarity, milliequivalent, molecular weight, displacement titration, blank determination, titer value.

Q5.2. Suggest a general assay procedure for the following types of compounds: an alkaloidal salt, sodium salt of an organic acid, alkaloid base, ester, amino acid, compound containing acetylenic hydrogen, water-insoluble organic acid, acetate of a high molecular weight alcohol.

Q5.3. Show by balanced equations the chemical reactions involved in the assay of the following official compounds: aluminum phosphate gel, chloral hydrate, methenamine, potassium sodium tartrate, benzaldehyde, morphine sulfate, theobromine sodium acetate, methyl salicylate.

Q5.4. Discuss in detail the mechanism by which indicators function in detecting the end point in titrations.

Q5.5. Why is methyl red used as the indicator in the assay of magnesia magma in preference to phenolphthalein or methyl orange?

Q5.6. Suggest a suitable indicator for the following titrations: ammonium hydroxide with hydrochloric acid, salicylic acid with sodium hydroxide, sodium bicarbonate with sulfuric acid, propylhexedrine with hydrochloric acid, bithionol with potassium hydroxide.

Q5.7. What is the advantage of using a mixed indicator? Mention several assay procedures which employ a mixed indicator.

Q5.8. Explain why methyl orange, methyl red, or phenolphthalein may be used as the indicator in the titration of a strong acid with a strong base, whereas of these three indicators only phenolphthalein may be employed in the titration of a weak acid with a strong base.

Q5.9. Discuss the nature of the titration curve obtained when a weak acid is titrated with a strong base.

Q5.10. What are the properties of an ideal primary standard? Mention several primary standards and indicate the advantages and disadvantages of each.

Q5.11. What are the advantages and disadvantages in using barium hydroxide as a standard base?

Q5.12. When is residual titration effective where direct titration fails?

Q5.13. Why is the assay of lactic acid a residual titration procedure?

Q5.14. Why in the preparation of standard sodium hydroxide is it necessary to avoid carbonate formation?

Q5.15. Why is sucrose used in the BP assay for calcium hydroxide?

Q5.16. What is the purpose of sodium lauryl sulfate in the assay of salicylic acid collodion?

Q5.17. In the assay of sodium biphosphate, USP, why is saturated solution of sodium chloride added to the titration mixture?

Q5.18. Why is alcohol used as the solvent in the assay of salicylic acid?

Q5.19. What is the purpose of ammonium chloride in the assay of zinc oxide?

Q5.20. Why is standard sulfuric acid preferred to hydrochloric acid in the assay of methenamine?

Q5.21. Why cannot alkali salts of organic acids such as sodium citrate and sodium acetate be assayed by direct titration as in the assays of sodium carbonate and sodium borate?

Q5.22. Indicate several official assay procedures involving a potentiometric titration. When is it necessary to resort to potentiometric titration in an assay?

Q5.23. Explain how ion exchange resins may be employed in the analysis of alkaloidal salts and salts of organic acids.

Q5.24. Explain the stepwise assay procedure for the following official compounds: chloral hydrate USP and BP; tolbutamide, USP; mechlorethamine hydrochloride, USP; busulfan, USP; meprobamate, NF and BP; aluminum acetate solution, USP; sodium salicylate, USP; methenamine, NF; tribasic calcium phosphate, NF; borax, BP; benzaldehyde, NF; boric acid, USP and BP; propylthiouracil, USP; triethylenemelamine, NF; ephedrine hydrochloride, NF.

Q5.25. Each milliliter of 0.1 *N* sodium hydroxide is equivalent to how many milligrams of the following official products: acetic acid, benzoic acid, hexachlorophene, boric acid, potassium bitartrate, glutamic acid hydrochloride, carboxyl groups as in the assay of oxidized cellulose, methimazole, borax as in BP assay, formaldehyde in formaldehyde solution, sucrose octaacetate as in alcohol rubbing compound, sodium dihydrogen phosphate (phenolphthalein end point).

Q5.26. Each milliliter of 0.1 *N* sulfuric acid is equivalent to how many milligrams

of the following official products: sodium hydroxide, ephedrine sulfate in ephedrine sulfate capsules, potassium citrate, zinc oxide, sodium carbonate (methyl orange end point), methenamine, magnesia magma, sodium salicylate, sodium borate, lidocaine, primidone, magnesium oxide.

## PROBLEMS

P5.1. (a) How many grams of $H_2SO_4$ are there in 150 ml of a 0.75 *N* solution?
(b) How many milligrams of NaOH are equivalent to 15 ml of 0.5 *N* HCl?
(c) How many milliliters of 0.25 *N* NaOH will react with 262 mg of benzoic acid?
(d) How many milliequivalents of $H_2SO_4$ are there in 125 ml of 0.675 *N* solution?
(e) How many milliliters of 1.25 *N* NaOH are equivalent to 50 ml of 0.75 *M* $H_2SO_4$?

P5.2. (a) How many milliliters of 0.5 *N* HCl are needed to prepare 450 ml of a 0.125 *N* solution?
(b) If 42.25 ml of 0.25 *N* HCl is required to neutralize 35.00 ml of sodium hydroxide solution, what is the normality of the latter solution?
(c) What is the normality of a solution which contains 15.750 g of NaOH in 0.5 liter of solution?
(d) How many milliliters of 0.125 *N* HCl are required to neutralize 25 ml of 0.0950 *N* NaOH solution?
(e) What is the normality of a sodium hydroxide solution if in standardization of the solution 16.23 ml is required to neutralize 352.1 mg of potassium acid phthalate?

P5.3. Magnesia magma was assayed by dissolving a sample weighing 4.9950 g in exactly 25 ml of 0.9976 *N* $H_2SO_4$. The excess acid was titrated with 1.0250 *N* NaOH to a methyl red end point. The back titration required 11.66 ml. Calculate the $Mg(OH)_2$ content of the magma.

P5.4. A sample of sodium hydroxide, weighing 1.2661 g, required 28.55 ml of 1.0550 *N* sulfuric acid when titrated to a phenolphthalein end point. An additional 0.80 ml was required when titration was continued to a methyl orange end point. Calculate the per cent content of sodium hydroxide and sodium carbonate in the sample for analysis.

P5.5. A mixture consisting of 0.3750 g of $Na_2CO_3$ and 0.6250 g of $NaHCO_3$ is titrated with 0.9860 *N* $H_2SO_4$ solution. What volume of acid is required for the phenolphthalein end point? What total volume of acid is required for the methyl orange end point?

P5.6. A sulfuric acid solution was standardized gravimetrically by precipitating the sulfate as $BaSO_4$. If 20 ml of the sulfuric acid solution yielded a precipitate which weighed 0.2654 g, what is the normality of the acid?

P5.7. A solution of HCl was standardized against primary standard sodium carbonate to a methyl orange end point. The sample weight of the sodium carbonate was 0.3495 g and required for neutralization 25.26 ml of acid. What is the normality of the HCl solution?

P5.8. A sample of hydrochloric acid weighing 3.8321 g is titrated with 1.0870 *N*

sodium hydroxide. If the hydrochloric acid has a percentage purity of 36.75%, what volume of base should be required in the titration?

P5.9. Twenty (five-grain) acetylsalicylic acid tablets after powdering weighed 10.5250 g. A sample of the powder weighing 0.8105 g was assayed as directed by the USP. After the solution was titrated to a phenolphthalein end point with 0.1 *N* NaOH, exactly 45 ml of 0.1 *N* NaOH (corrected volume on basis of blank) was added, and the mixture was heated in a bath of boiling water for 15 min. The solution was titrated with 0.1 *N* $H_2SO_4$ to a phenolphthalein end point and required 17.22 ml. Calculate the acetylsalicylic acid content of each tablet. Assume that 1 grain equals 65 mg.

P5.10. A sample of methadone hydrochloride weighing 0.1405 g was extracted with ether from an alkaline solution. The extract was treated with 30 ml of 0.0192 *N* $H_2SO_4$. The excess acid was titrated with 0.0210 *N* NaOH to a methyl red end point and required 8.27 ml in the titration. Calculate the percentage purity of the methadone hydrochloride.

P5.11. A sample of ethyl acetate weighing 1.4560 g was treated with 50 ml of 0.4996 *N* NaOH as described in the NF assay procedure. In the back titration with 0.5186 *N* HCl, 16.70 ml was required for a phenolphthalein end point. In the blank determination 48.17 ml of the standard acid was consumed. Calculate the per cent purity of the ethyl acetate.

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