Analytical chemistry

Lecture №18

Acid-base Titrations in Non-aqueous Solvents

TITRATION

A reaction conducted by slow addition of a precisely measured volume of a **reagent** solution of known concentration

to

an amount of another **substance***

until

a ***SIGNAL*** indicates that reaction between **reagent** and **substance** is complete

SIGNAL is often a **COLOR CHANGE**, but may be an observable change in another property.

* with which it is known to react

In order to overcome these shortcomings the non-aqueous titrations were introduced.

Non-aqueous titrations have the following **advantages, namely :**

- Elimination of poor solubility of substances,
- Enhancement of weak reactivity of substances,
- Selective titration by using suitable solvent and titrant of acidic/basic components of physiologically active moiety of a salt,
- Maintenance of speed, precision, accuracy and simplicity at par with classical methods of analysis, and
- Weak bases which have K_b *values less than* 10^{-6} *can be titrated satisfactorily by non-aqueous* titrations. The reason being that in aqueous medium and at higher K_b *values (>* 10^{-6}*) the solvent* water competes progressively with the basic species in solution for the proton of the solvent.

THEORY

The concepts of the Lowry-Bronsted theory may explain the various reactions that take place during many non-aqueous titrations. Thus, an *acid is a* ***proton donor and a base is a proton acceptor. Therefore,*** when an acid HA undergoes dissociation it gives rise to a proton and the conjugate base A of the acid :

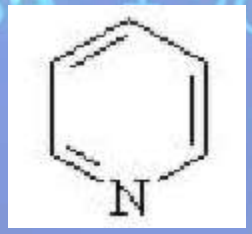
$$\underset{\text{Acid}}{HA} \rightleftharpoons \underset{\text{Proton}}{H^+} + \underset{\text{Base}}{A^-}$$

In other words, the liberated base A^- shall unite with a proton to give the corresponding conjugate acid HA of the base A^- because every base has its conjugate acid and *vice versa.*

Hence, from the above definitions it may be implied that:
(*a)* an acid: could be either an electrically neutral molecule e.g., HNO_3; or a negatively charged anion *e.g., HSO_4^-*; or a positively charged cation *e.g., $C_6H_5NH_2^+$*, H_3O^+;
(*b)* a base: could be either an electrically neutral molecule e.g., $C_6H_5NH_2$; or an anion e.g., Cl^-, NO_3^-.

Substances which give poor end points due to being weak acids or bases in aqueous solution will frequently give far more satisfactory end points when titrations are carried out in non-aqueous media. An additional advantage is that many substances which are insoluble in water are sufficiently soluble in organic solvents to permit their titration in these non-aqueous media. The ability of substances to act as acids or bases will depend very much upon the nature of the solvent system which is employed. Non-aqueous solvents are classified into the four groups: ***aprotic*** solvents, ***protophilic*** solvents, ***protogenic*** solvents, and ***amphiprotic*** solvents.

SOLVENTS



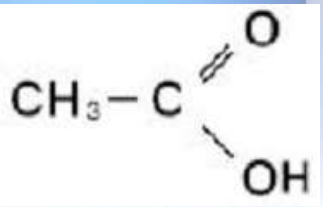
pyridine, liq. NH_3, amins, dioxane

• **Protophillic Solvents** : substances such as liquid ammonia, amines and ketones which possess a high affinity for protons. They are essentially **basic** in nature and normally react with acids to form solvated protons:

$$HA + Sol. \rightleftharpoons Sol.\ H^+ + A^-$$

Acid	Basic solvent	Solvated proton	Conjugate base of acid

The equilibrium in this reversible reaction will be greatly influenced by the nature of the acid and that of the solvent. Weak acids are normally used in the presence of strongly protophilic solvents as their acidic strengths are then enhanced and then become comparable to those of strong acids -- this is referred to as the ***'levelling effect'.***



• **Protogenic Solvents :** They are **acidic** in nature and character *e.g., sulphuric acid.* They exert *a* '*levelling effect'* on bases i.e., they become indistinguishable in strength when dissolved in strongly basic solvents due to their enhanced affinity of strong bases for protons.

H_2SO_4, CH_3COOH, HCOOH, acetone

Amphiprotic Solvents: They possess both *protophillic and protogenic characteristics.*

Examples: Acetic acid, water and alcohols.

They undergo dissociation to a very less extent. Acetic acid is mostly employed as a solvent for the titration of basic substances and its dissociation can be depicted as shown below :

$$CH_3COOH \rightleftharpoons H^+ + CH_3COO^-$$

But in the presence of perchloric acid, which is a far stronger acid, acetic acid will accept a proton:

$$HClO_4 \rightleftharpoons H^+ + ClO_4^-$$

$$CH_3COOH + H^+ \rightleftharpoons CH_3COOH_2^+$$

Onium ion

The $CH_3COOH_2^+$ - ion so formed can very readily give up its proton to react with a base. A weak base will, therefore, have its basic properties enhanced, and as a consequence titrations between weak bases and perchloric acid can frequently be readily carried out using acetic acid as solvent.

INERT: CCl_4, $CHCl_3$, benzene, carbohydrates

Pyridine, a weak base, when dissolved in acetic acid, the latter exerts its ***levelling effect*** and subsequently increases the basic characteristics of the pyridine. Therefore, it is practically feasible to titrate a solution of a weak base in acetic acid against a mixture of perchloric acid in acetic acid. Thus, a sharp end point is achieved which otherwise cannot be obtained when the titration is performed in an aqueous medium.

The various reactions with perchloric acid, acetic acid and pyridine are summarized below :

$$HClO_4 + CH_3COOH \rightleftharpoons CH_3COOH_2^+ + ClO_4^-$$

$$C_6H_5N + CH_3COOH \rightleftharpoons C_6H_5NH^+ + CH_3COO^-$$

$$CH_3COOH_2^+ + CH_3COO^- \rightleftharpoons 2CH_3COOH$$

Summing up : $HClO_4 + C_6H_5N \rightleftharpoons C_6H_5NH^+ + ClO_4^-$

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leveling

Acids that are better proton donors than the solvent are leveled to the acid strength of the protonated solvent; bases that are better proton acceptors than the solvent are leveled to the base strength of the deprotonated solvent.

All other things being equal, the strength of a weak acid increases if it is placed in a solvent that is more basic than water, whereas the strength of a weak base increases if it is placed in a solvent that is more acidic than water.

The dissociation, or autoprotolysis constant for a solvent, SH, relates the concentration of the protonated solvent, SH_2^+, to that of the deprotonated solvent, S^-. For amphoteric solvents, which can act as both proton donors and proton acceptors, the autoprotolysis reaction is

$$2SH \rightleftharpoons SH_2^+ + S^-$$

with an equilibrium constant of

$$K_s = [SH_2^+][S^-]$$

pH scale depends on the value of

The pH of a solution is now seen to be a general statement about the relative abundance of protonated solvent

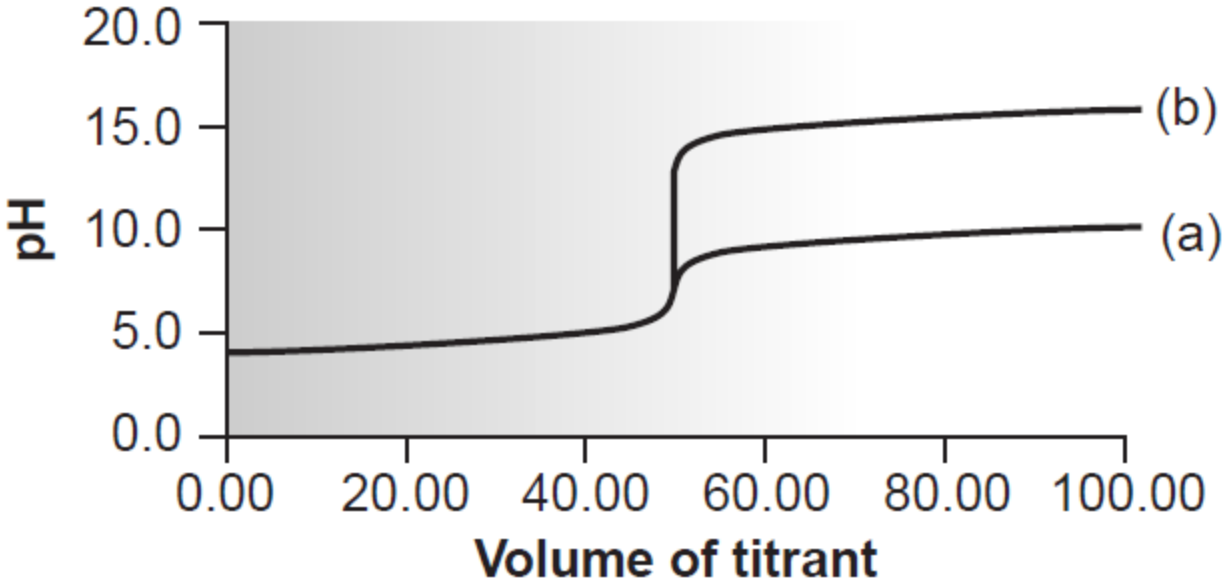
$$pH = -\log[SH_2^+]$$

where the pH of a neutral solvent is given as

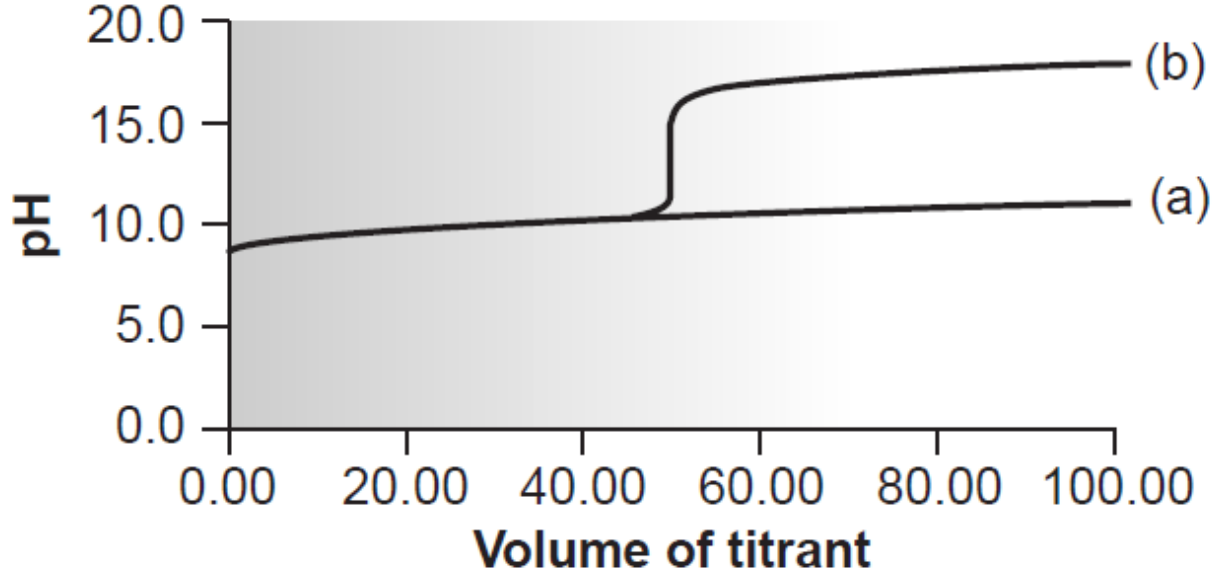
$$pH_{neut} = \frac{1}{2} pK_s$$

solvent	K	pH scale	neutr. point
$2\,H_2O \leftrightarrows H_3O^+ + OH^-$	10^{-14}	0 - 14	7
$2\,CH_3COOH \leftrightarrows CH_3COH_2^+ + CH_3COO^-$	10^{-13}	0 - 13	6,5
$2\,NH_3 \leftrightarrows NH_4^+ + NH_2^-$	10^{-32}	0 - 32	16
$2\,C_2H_5OH \leftrightarrows C_2H_5OH_2^+ + C_2H_5O^-$	10^{-19}	0 - 19	9,5

You should be aware, however, that titrations that are not feasible in water may be feasible in a different solvent.



Titration curves for 50.00 mL of 10^{-4} M HCl with 10^{-4} M NaOH in **a)** water, $K_w = 10^{-14}$, *and* **b)** *nonaqueous solvent,* $K_s = 10^{-20}$.



Titration curves for 50.00 mL of 0.100 M weak acid (pK_a= *11) with 0.100 M NaOH in* **a)** water, *Kw =*10^{-14}*; and* **b)** nonaqueous solvent, K_s =10^{-20}.

Nonaqueous solvents also may be used to increase the change in pH when titrating weak acids or bases

SOLVENTS FOR NON-AQUEOUS TITRATIONS

Glacial acetic acid (ethanoic acid) is by far the most frequently employed solvent for this purpose. Before it is used it is advisable to check the water content, which may be between 0.1 and 1.0%, and to add just sufficient acetic anhydride to convert any water to the acid. The acid may be used by itself or in conjunction with other solvents such as acetic anhydride, acetonitrile and nitromethane.

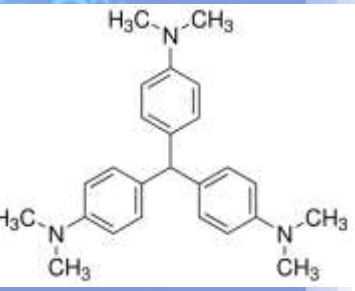
Acetonitrile (methyl cyanide, cyanomethane) is frequently used with other solvents such as chloroform and phenol, and particularly with acetic acid. It enables very sharp end points to be obtained in the titration of metal acetates when titrated with perchloric acid.

Alcohols: it has been found that determinations of salts of organic acids and especially of soaps are best carried out in solvent mixtures of glycols and alcohols or of glycols and hydrocarbons. The most common combinations of this type are ethylene glycol (dihydroxyethane) with propan-2-ol or butan-l-ol. The combinations provide admirable solvent power for both the polar and non-polar ends of the molecule. Another suitable solvent mixture is methanol and benzene.

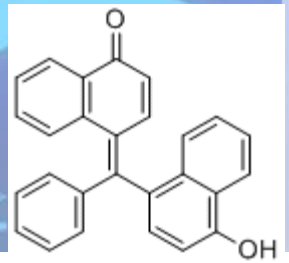
Dioxan is another popular solvent which is often used in place of glacial acetic acid when mixtures of substances are to be quantified. Unlike acetic acid, dioxan is not a levelling solvent and separate end points are normally possible corresponding to the individual components in the mixtures.

Dimethylformamide (DMF) is a protophilic solvent which is frequently employed for titrations between, for instance, benzoic acid and amides, although end points may sometimes be difficult to obtain.

INDICATORS FOR NON-AQUEOUS TITRATIONS

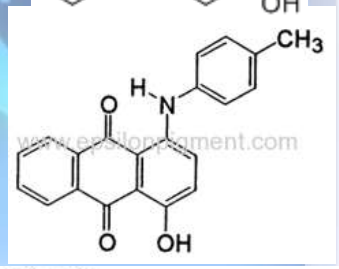


(a) ***Crystal violet*** is used as a 0.5 per cent w/v solution in glacial acetic acid. Its colour change is from violet through blue, followed by green, then to greenish-yellow, in reactions in which, for instance, bases such as pyridine are titrated with perchloric acid.

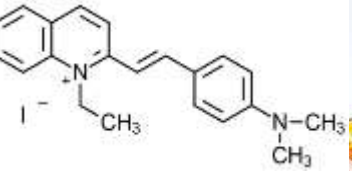


(b) ***Methyl red*** is used as a 0.2 per cent w/v solution in dioxan with a yellow to red colour change.

(c) ***1-Naphthol benzein*** gives a yellow to green colour change when employed as a 0.2 per cent w/v solution in acetic acid. It gives sharp end points in nitromethane containing acetic anhydride for titrations of weak bases against perchloric acid.



(d) ***Oracet blue B*** is used as a 0.5 per cent w/v solution in acetic acid and is considered to be superior to crystal violet for titrations of bases in acetic acid with standard perchloric acid. The end point is a distinct change from blue to pink.



(e) ***Quinaldine red*** has been used as an indicator for drug determinations in dimethylformamide solution. It is used as a 0.1 per cent w/v solution in ethanol and gives a colour change from purple/red to pale green.

(f) ***Thymol blue*** is used extensively as an indicator for titrations of substances acting as acids in dimethylformamide solution. It is used as a 0.2 per cent w/v solution in methanol with a sharp colour change from yellow to blue at the end point.

Name of Indicator	Colour-change observed		Acidic
	Basic	Neutral	
Crystal violet (0.5% w/v in glacial acetic acid)	Violet	Blue-green	Yellowish green
Oracet Blue B (0.5% in glacial acetic acid)	Blue	Purple	Pink
α-Naphtholbenzein (0.2% in glacial acetic acid)	Blue or blue green	Orange	Dark-green
Quinalidine Red (0.1% in methanol)	Magenta	—	Almost colourless

Assays of various pharmaceutical substances either in pure form or in dosage form may be assayed successfully by non-aqueous titrations. For the sake of convenience these typical titrations can be categorized into two broad groups, namely:

I. Acidimetry in Non-aqueous Titrations—It can be further sub-divided into two heads, namely: a) Titration of primary, secondary and tertiary amines, and b) Titration of halogen acid salts of bases.

II. Alkalimetry in Non-aqueous Titrations—i.e., titration of acidic substances.

Crystal violet

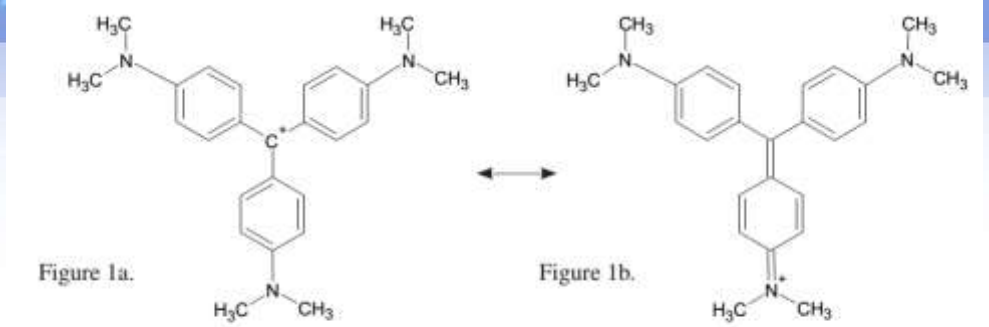
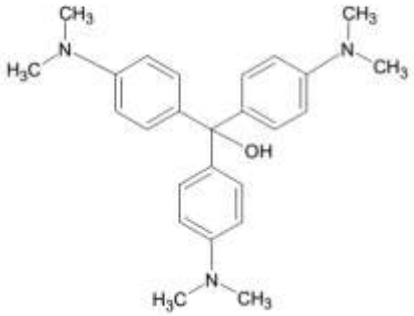
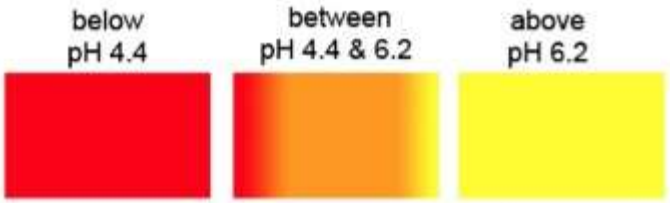


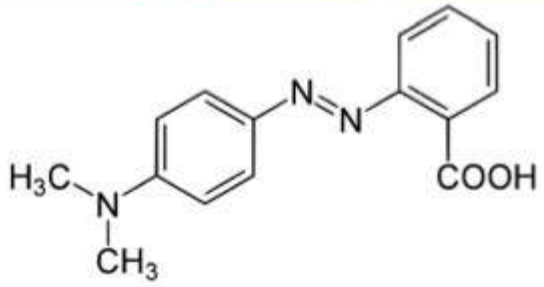
Figure 1a. Figure 1b.

Figure 1.

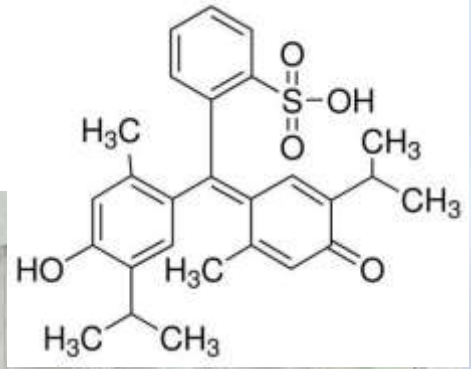


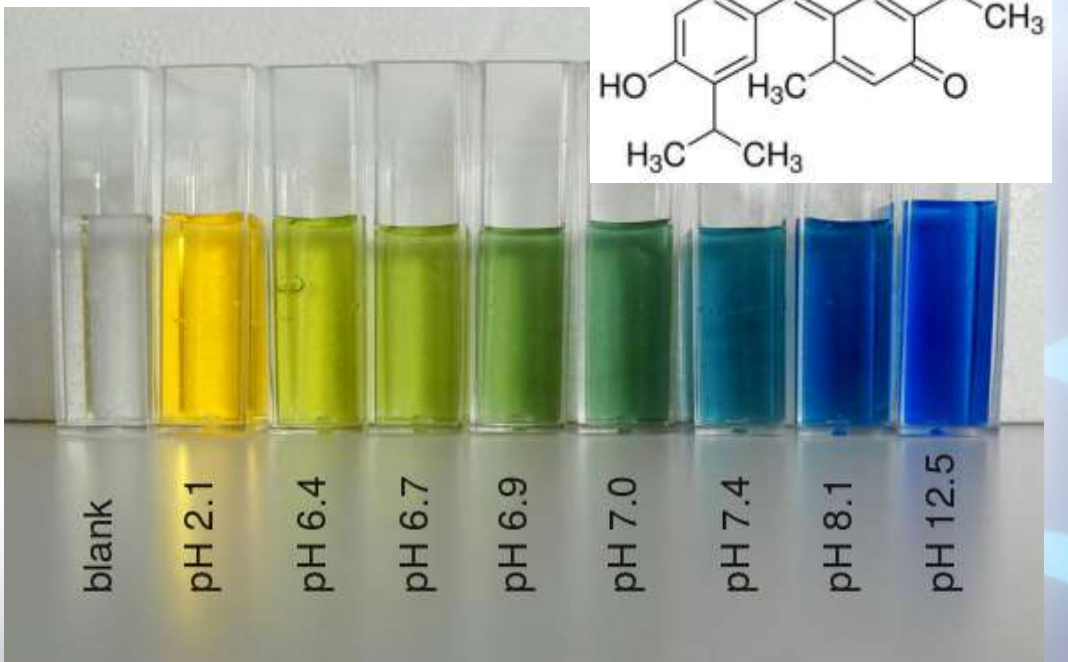
Methyl red indicator color





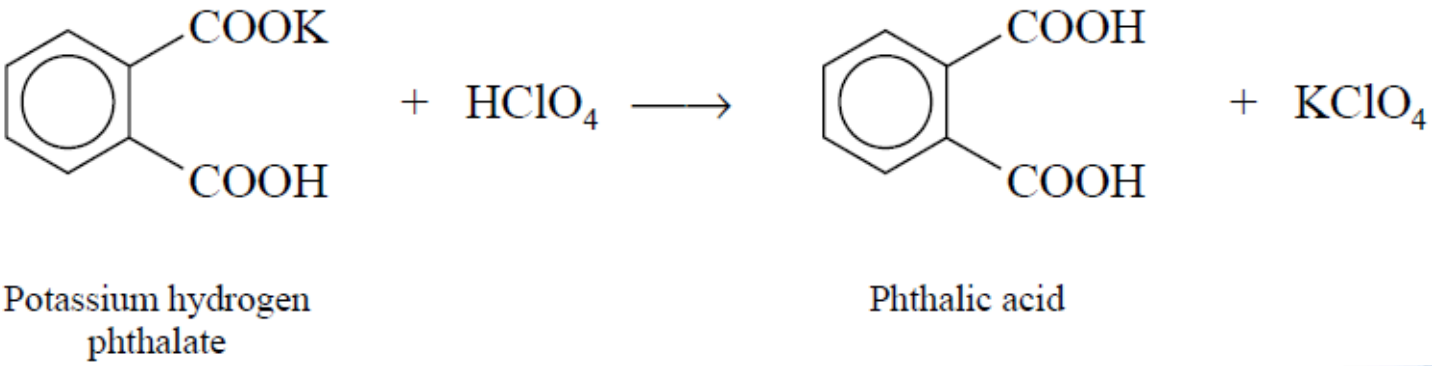
Thymol blue





STANDARDIZATION OF 0.1 M PERCHLORIC ACID

In usual practice, potassium hydrogen phthalate (or potassium biphthalate, $KHC_8H_4O_4$) is employed as a standardizing agent for acetous perchloric acid. The reaction may be expressed as follows



Potassium hydrogen phthalate

Phthalic acid

Procedure : Weigh accurately about 0.5 g of potassium hydrogen phthalate in a 100 ml conical flask. Add 25 ml of glacial acetic acid and attach a reflux condenser fitted with a silica-gel drying tube. Warm until the salt gets dissolved completely. Cool and titrate with 0.1 N perchloric acid by making use of either of the following *two indicators :*

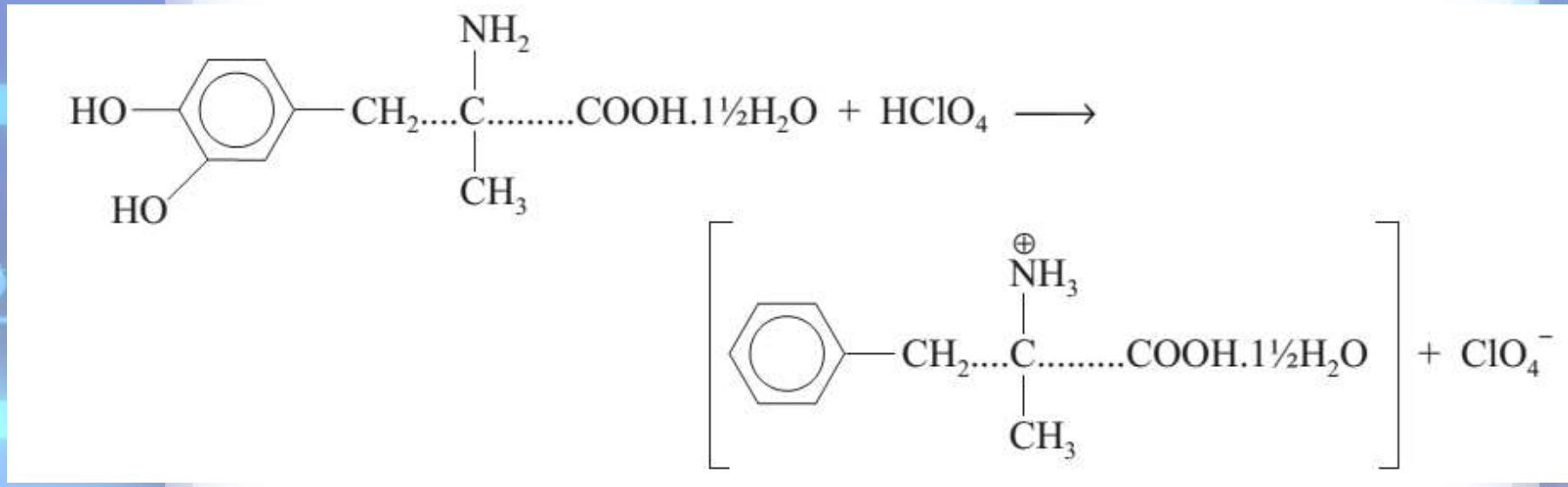
(a) acetous crystal violet-2 drops, end point Blue to Blue-Green (0.5% w/v)

(b) acetous oracet blue B-2 drops, end point Blue to Pink.

ACIDIMETRY IN NON-AQUEOUS TITRATIONS

Titration of primary, secondary and tertiary amines

The specific reaction between methyldopa and perchloric acid is expressed by the following equation



Materials Required: Methyldopa 0.2 g; anhydrous formic acid : 15 ml; glacial acetic acid: 30 ml; dioxane : 30 ml; 0.1 M perchloric acid and crystal violet solution.

Procedure: Weigh accurately about 0.2 g and dissolve in 15 ml of anhydrous formic acid, 30 ml of glacial acetic acid and 30 ml of dioxane. Add 0.1 ml of crystal violet solution and titrate with 0.1 M perchloric acid. Perform a blank determination and make any necessary correction. Each ml of 0.1 M perchloric acid is equivalent to 0.02112 g of $C_{10}H_{13}NO_4$.

Titration of Halogen Acid Salts of Bases

In general, the halide ions, namely: chloride, bromide and iodide are very weakly basic in character so much so that they cannot react quantitatively with acetous perchloric acid. In order to overcome this problem, mercuric acetate is usually added (it remains undissociated in acetic acid solution) to a halide salt thereby causing the replacement of halide ion by an equivalent amount of acetate ion, which serves as a strong base in acetic acid as shown below:

$$2R.NH_2.HCl \rightleftharpoons 2RNH_3^+ + 2Cl^-$$

$$(CH_3COO)_2Hg + 2Cl^- \longrightarrow HgCl_2 + 2CH_3COO^-$$

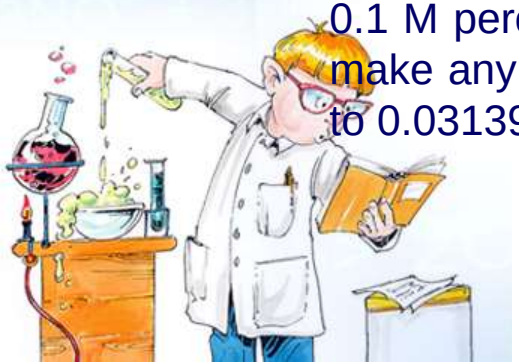
undissociated undissociated

$$2CH_3COOCH_2^+ + 2CH_3COO^- \rightleftharpoons 4\ CH_3COOH$$

Amitriptyline Hydrochloride

Materials Required: Amitriptyline hydrochloride: 1.0 g; mercuric acetate; crystal violet ; 0.1 M perchloric acid; glacial acetic acid.

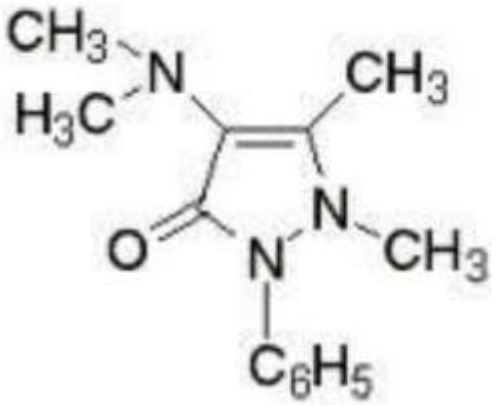
Procedure: Weigh accurately about 1.0 g and dissolve in 50 ml of glacial acetic acid, warming slightly, if necessary, to affect the solution. Cool, add 10 ml of mercuric acetate solution, two drops of crystal violet solution and titrate with 0.1 M perchloric acid to a green end-point. Perform a blank determination and make any necessary correction. Each ml of 0.1 M perchloric acid is equivalent to 0.03139 g of $C_{20}H_{23}N$. HCl. Equations:



$$2C_{20}H_{23}N.HCl \rightleftharpoons 2C_{20}H_{23}N, H^+ + 2Cl^-$$

$$(CH_3COO)_2\ Hg + 2Cl^- \longrightarrow HgCl_2 + 2CH_3COO^-$$

$$2\ CH_3COOH_2^+ + 2CH_3COO^- \rightleftharpoons 4CH_3COOH$$



CH_3COOH

solvent

Amidopyrine – is a very weak organic base with $K_a = 10^{-9}$, which cannot be titrated in an aqueous solution. When a weak base, such as amidopyrine, is dissolved in acetic acid, the acetic acid exerts its levelling effect and enhances the basic properties of the amidopyrine. It is possible, therefore, to titrate a solution of a weak base in acetic acid with perchloric acid, and obtain a sharp endpoint when attempts to carry out the titration in aqueous solution are unsuccessful.

ALKALIMETRY IN NON-AQUEOUS TITRATIONS

A plethora of weakly acidic pharmaceutical substances may be titrated effectively by making use of a suitable non-aqueous solvent with a sharp end-point. The wide spectrum of such organic compounds include: anhydrides, acids, amino acids, acid halides, enols (viz., barbiturates), xanthines, sulphonamides, phenols, imides and lastly the organic salts of inorganic acids. However, a weak inorganic acid e.g., boric acid, can be estimated conveniently employing ***ethylenediamine*** as the non-aqueous solvent.

There are several drugs which are weakly acidic. Such substances can be titrated against strong bases like potassium methoxide, sodium methoxide, lithium methoxide, tetra butyl ammonium hydroxide, etc in solvents like toluene- methanol. The principle is similar to the titration of weak bases against perchloric acid.

Preparation of 0.1 M Potassium Methoxide in Toluene-Methanol

Materials Required: Absolute methanol: 40 ml; dry toluene: 50 ml; potassium metal: 4 g.

Procedure: Add into a dry flask, a mixture of methanol (40 ml) and dry toluene (50 ml) and cover it loosely. Carefully add freshly cut pieces of potassium metal to the above mixture gradually with constant shaking. After complete dissolution of potassium metal, add enough absolute methanol to yield a clear solution. Toluene 50 ml is added with constant shaking until the mixture turns hazy in appearance. The process is repeated by the alternate addition of methanol and benzene until 1 litre of solution is obtained, taking care to add a minimum volume of methanol to give a visible clear solution.

Standardization of 0.1 M Methoxide Solution

Materials Required: Dimethylformamide (DMF): 10 ml; thymol blue (0.3% in MeOH); 0.1 M lithium methoxide in toluene methanol; benzoic acid : 0.6 g.

Procedure: Transfer 10 ml of DMF in a conical flask and add to it 3 to 4 drops of thymol blue and first neutralize the acidic impurities present in DMF by titrating with 0.1 M lithium methoxide in toluene-methanol. Quickly introduce 0.06 g of benzoic acid and titrate immediately with methoxide in toluene methanol.

$$C_6H_5COOH + \underset{\text{DMF}}{H{-}CON(CH_3)_2} \rightleftharpoons HCON^+H(CH_3)_2 + C_6H_5COO^-$$

$$CH_3ONa \rightleftharpoons CH_3O^- + Na^+$$

$$HCON^+H(CH_3)_2 + CH_3O^- \longrightarrow HCON(CH_3)_2 + CH_3OH$$

Summing up : $C_6H_5COOH + CH_3ONa \longrightarrow C_6H_5COONa + CH_3OH$

Preparation of 0.1 M Tetrabutylammonium Hydroxide in Toluene-Methanol

Materials Required: Tetrabutylammonium iodide: 40 g; absolute methanol: 90 ml ; silver oxide: 25 g; dry toluene: 150 ml.

$$\underset{\text{Tetrabutyl-ammonium bromide}}{2Bu_4NI} + Ag_2O + H_2O \longrightarrow \underset{\text{Tetrabutyl ammonium hydroxide}}{2Bu_4NOH} + 2AgI$$

Standardization of 0.1 M Tetrabutylammonium Hydroxide

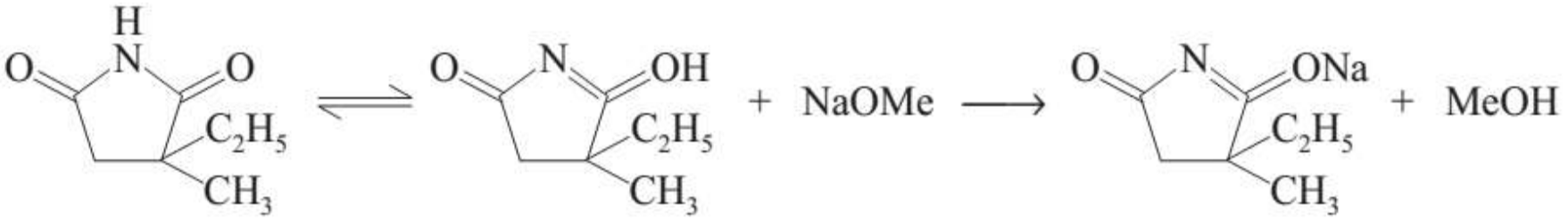
Materials Required: Benzoic acid: 60 mg; dimethylbromide: 10 ml; thymol blue solution (0.3% w/v in methanol); 0.1 M tetrabutylammonium hydroxide.

Procedure: Accurately weigh about 60 mg of benzoic acid into 10 ml of previously neutralized dimethyl formamide to the blue colour of thymol blue (3 drops) by titration against 0.1 M tetrabutylammonium hydroxide. Allow the benzoic acid to dissolve gradually and completely and titrate with 0.1 M tetrabutylammonium hydroxide preferably in an atmosphere of CO_2-free nitrogen.

Ethosuximide

Materials Required : Ethosuximide: 0.2 g; dimethylformamide: 50 ml; azo-violet (0.1% w/v in DMF): 2 drops; sodium methoxide 0.1 M.

Procedure: Weigh accurately about 0.2 g, dissolve in 50 ml of dimethylformamide, add 2 drops of azo-violet solution and tirate with 0.1 M sodium methoxide to a deep blue end point, taking precautions to prevent absorption of atmospheric carbon dioxide.

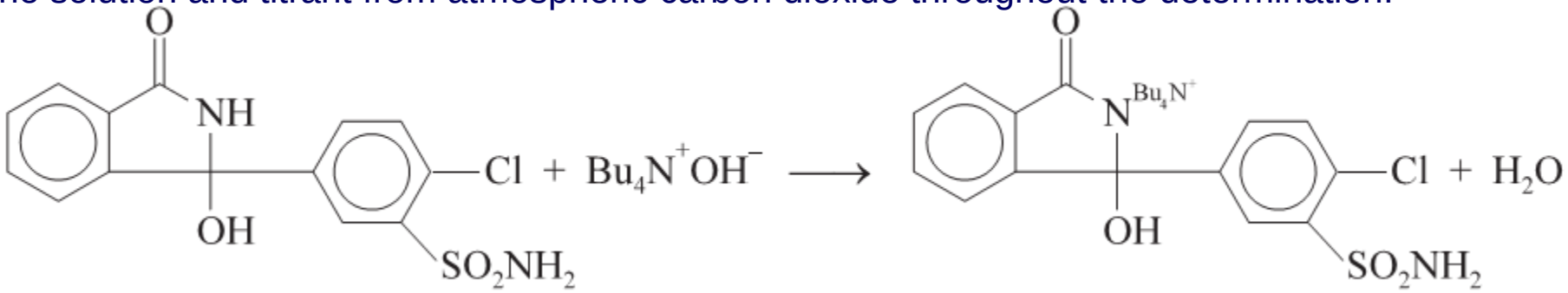


Ethosuximide (*keto*-form) | Ethosuximide (*enol*-form) | Sodium salt of Ethosuximide

Chlorthalidone

Materials Required: Chlorthalidone: 0.3 g; pyridine (dehydrated): 50 ml; 0.1 M tetrabutylammonium hydroxide.

Procedure : Weigh accurately about 0.3 g and dissolve in 50 ml of dehydrated pyridine. Titrate with 0.1 M tetrabutylammonium hydroxide, determining the end point potentiometrically and protecting the solution and titrant from atmospheric carbon dioxide throughout the determination.



ADVANTAGES OF NON AQUEOUS SOLVENT OVER AQUEOUS SOLVENT:

1) Organic acids and bases that are insoluble in water are soluble in non-aqueous solvent.

2) Organic acid, which is of comparable strength to water, can be titrated easily in nonaqueous solvent. Bases also follow the same rules.

3) A non-aqueous solvent may help two are more acids in mixture. The individual acid can give separate end point in different solvent.

4) By the proper choice of the solvents or indicator, the biological ingredients of a substance whether acidic or basic can be selectively titrated.

5) Non aqueous titrations are simple and accurate, examples of non aqueous titration are: Ephedrine preparations, codeine phosphate in APC, tetracycline, teramycin, Antihistamines and various piprazine preparations.

DISADVANTAGES of USING NON-AQUEOUS SOLVENTS

1) expensive
2) volatile
3) toxic
4) removal of water is necessary, can take water (humidity) from the air