

2.3. NON-AQUEOUS TITRATION

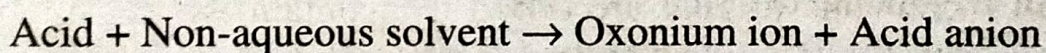
Titration involving very weak acid or base, with the help of non-aqueous solvents, to obtain sharp end point are **non-aqueous titrations**. These titrations are used for titrating water insoluble substances. While comparing with the conventional acid base titrations, i.e., acidimetric and alkalimetric titrations, the speed, accuracy, and precision of non-aqueous titrations do not lack behind.

The procedure of non-aqueous titrations involves the same apparatus, but presence of carbon dioxide and moisture must be avoided. This is because water acts as a weak base and competes with weak nitrogen bases, resulting in end point which is not sharp.

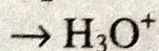
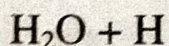
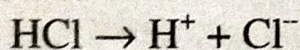
2.3.1. Principle

Organic acids and bases are water insoluble, very weak, and cannot be analysed via conventional titration methods; thus, non-aqueous titration is used which relies on the principle that non-aqueous solvents are used to dissolve the samples.

Let us consider an **example of glacial acetic acid** reacting with water and forming **oxonium ion** (in low concentration). This can be prevented and ions of high concentration can be yielded by dissolving glacial acetic acid in a non-aqueous solvent.



As per the Bronsted-Lowry theory, acid is the substance donating proton and base is the substance accepting proton.



Thus, the strength of an acid or a base can be estimated by their affinity to donate or accept protons.

2.3.2. Non-Aqueous Solvents

The nature of solvent is a deciding factor for the behaviour of acids and bases. Any solute when dissolved in any given solvent will exhibit acidic or alkaline behaviour, which solely depends on the following properties of solvent:

- 1) The property of solvent (either acidic or basic) is related to the solute,
- 2) The constant of auto-proteolysis of the solvent, and
- 3) Dielectric constant of the solvent used.

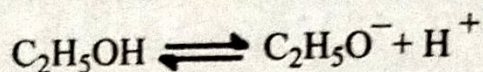
*Et → sol. ↑
ionic & polar*

The non-aqueous solvents have a characteristic role in non-aqueous titrations. Generally, the solvent should be non-toxic for its wide use in analysis; it should be liquid at the time of analysis. These organic solvents are used but it is mainly dependent on their properties such as capability of self-dissociation, dielectric constant, and acid-base character of solvent.

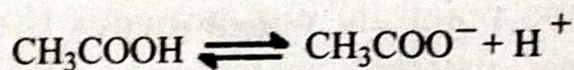
2.3.2.1. Dissociating and Non-Dissociating Solvents

Solvents can be classified as dissociating and non-dissociating solvents.

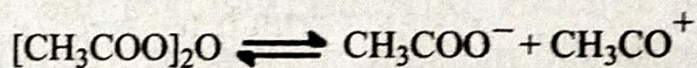
1) **Dissociating Solvents:** For example ethanol dissociates to give ethoxide ion:



Acetic acid gives acetate ion:



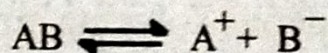
H^+ represents the solvated protons and its range varies with the solvent. Some solvents dissociate without the production of solvated protons, e.g., acetic anhydride.



It yields acetate and acetylum ion.

2) **Non-Dissociating Solvents:** These solvents may dissociate but it is not usually detectable. For example, ethers and hydrocarbons.

It is always possible to define ion product of dissociating solvent. The solvent is represented by AB:



The ion product (K_s) can be written as:

$$K_s = [\text{A}^+][\text{B}^-]$$

2.3.2.2. Acid-Base Character of a Solvent

Based on the proton donor-acceptor properties, the non-aqueous solvents can be classified. Four categories of non-aqueous solvents are protogenic, protophilic, aprotic, and amphiprotic solvents.

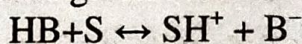
For example, AB is a dissociating solvent which dissociates to give the cation A^+ (lyonium ion) and the anion B^- (lyate ion). The lyonium ion is the species that gives the acidic nature to the solvent, while lyate ion provides the basic properties.

This concept states that **acid** is any substance which on dissolving in a dissociating solvent enhances the concentration of **lyonium ion**, **base** is any substance which promotes the **lyate ion** concentration.

The solvents are of the following four types as mentioned above:

1) **Aprotic Solvents:** These solvents are considered chemically neutral or inert under specific conditions, e.g., toluene and carbon tetrachloride. These solvents have low dielectric constants which restrict the ionisation of solutes and there is no reaction between these solvents and acids and bases. The aprotic solvents are widely used as diluting agent for the reaction mixture.

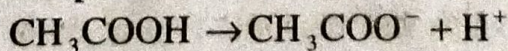
2) **Protophilic Solvents:** These solvents have high affinity for the protons. A generalised form of reaction is given below:



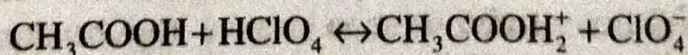
The equilibrium of the above stated reversible reaction is affected by the character of an acid, as well as, a solvent. The acidic character of weak acid gets enhanced in the presence of protophilic solvent. The acidic character is so strong that it can be compared to those of strong acids; this phenomenon is known as the **levelling effect**.

3) **Protophonic Solvents:** These solvents possess acidic character and have high affinity for donating protons. Protophonic solvents include anhydrous acids, such as hydrogen fluoride and sulphuric acid. Since these are strong acids, they act as proton donors resulting in the enhancement of the strength of weak bases.

4) **Amphiprotic Solvents:** Solvents like water, alcohols, and organic acids (weak) act as amphiprotic solvents, as they get feebly ionised and have the ability to donate, as well as, accept the protons, because they contain both protogenic and protophilic properties. The reaction depicted below shows the dissociation of ethanoic acid which produces protons and exhibits acidic nature:



While, in the presence of a stronger acid like perchloric acid, it acts as a proton acceptor:



$CH_3COOH_2^+$ ion donates proton instantly, which reacts with the base, thus, enhancing the basic characteristics of base. As a result, the titration between perchloric acid and a weak base can be done precisely with the help of ethanoic acid (solvent).

2.3.2.3. Frequently Used Solvents

For the determination of non-aqueous titrations there are several solvents available (either organic or inorganic) but only few of them are employed for the purpose. The solvents used must be pure, dry and of best analytical quality, to ensure precise and sharp end points.

The following solvents are frequently used while performing non-aqueous titrations:

- 1) **Glacial Acetic Acid:** This solvent is used most frequently as compared to other non-aqueous solvents. The water content of glacial acetic acid is analysed prior to use, which must be between 0.1-1.0%. In case the water content is more than the recommended amount, acetic anhydride is added which converts water into acid. The acid is used either alone or with some other solvents, such as acetic anhydride, acetonitrile, and nitro-methane.
- 2) **Acetonitrile:** This is cyano-methane or methyl cyanide and is used along with the other solvents like chloroform, phenol, etc. and especially with acetic acid. The titration of metallic ethanoates with perchloric acid gives accurate and sharp end points when acetonitrile is employed.
- 3) **Alcohols:** The organic salts of fatty acids can be determined with the help of glycol and alcohol mixtures, or glycol and hydrocarbon mixtures. Mixture of ethylene glycol and butan-1-ol or propan-2-ol is used most commonly, as these mixtures possess excellent solubilising power for both polar, as well as, non-polar molecules.
- 4) **Dioxane:** In case of quantitative analysis, dioxane is the solvent of choice to be used instead of acetic acid. The main reason for using dioxane is that it does not act as a levelling solvent (like acetic acid) and results in separate end points for the particular component present in the mixture.
- 5) **Dimethylformamide:** DMF is an excellent example of protophilic solvent and is used for the titration of benzoic acid and amides. Its major drawback is the lack of sharpness in the end point.

2.3.2.4. Advantages of Non-Aqueous Solvents over Aqueous Solvents

The non-aqueous solvents possess many advantages when compared to aqueous solvents:

- 1) The acids and bases of organic origin are easily soluble in non-aqueous solvents.
- 2) The titration of organic acid or base is not easy to perform in non-aqueous solvents because of the comparable strength of organic acid or base with that of water.
- 3) Non-aqueous solvents can dissolve two or more acids present in a mixture, thus giving distinct end point in different solvents.
- 4) With the help of a suitable solvent or indicator, the selective titration of biological ingredients present in a substance can be done, irrespective of whether it is acidic or basic.
- 5) Titrations involving non-aqueous solvents are comparatively simpler and more accurate than aqueous titrations. **Examples** of non-aqueous titrations are codeine phosphate in APC, tetracycline, teramycin, ephedrine preparations, anti-histamines and various piperazine preparations.

2.3.3. Indicators

The various resonant forms of indicator, whether ionised or unionised, do not affect non-aqueous titrations but there is variation of change in colour in different titrations, because of its dependence on titrant's nature. To ward off this problem, potentiometric titration is taken into account and the change in colour and the inflexion point are correlated in the titration curve. A very narrow range of indicators are present which are employed in non-aqueous titrations. Some of the examples of indicators are enlisted below:

- 1) **Crystal Violet:** A solution of crystal violet (0.5% w/v) is prepared using glacial acetic acid. The sequence of change in colour in titrations where pyridine is titrated using perchloric acid, starts from violet to blue, then to green and finally to greenish yellow. *0-1.8 Yellow to blue*
- 2) **Methyl Red:** A 0.2% w/v solution of methyl red is prepared using dioxane. The end point is marked by a change in colour from yellow to red. *4.8-6 Red-yellow*
- 3) **Naphthol Benzene:** Naphthol benzene is used as a solution of 0.2% in acetic acid. It gives a sharp end point by changing its colour from yellow to green. *8-10*
- 4) **Quinaldine Red:** This indicator found its application for the drug assays in a solution of Dimethyl Formamide (DMF). Its solution is prepared in ethyl alcohol by keeping a concentration of 0.1% w/v. The end point is detected by change in colour from purple red to pale green. *1-2.2 Col-red*
- 5) **Thymol Blue:** It is a widely used indicator especially for the substances behaving as acids in solution of DMF. 0.2% w/v solution is prepared using methyl alcohol and the end point is detected by change in colour from yellow to blue. *1.2-2.8, 8-9.6 Red-yellow ye-Blue*

2.3.4. Applications

The applications of non-aqueous titrations are:

- 1) **Percentage of Purity is Determined by the Assays:** For example, the sulphonilamide is dissolved in 50ml of dimethylformamide and 5 drops of thymol blue indicator. Resulting solution is titrated with sodium methoxide and the end point is detected as a blue colour.

$$\text{Percentage of sulphonilamide} = \frac{A \times N \times EW}{W \times 10}$$

Where,

A = Milliliters of sodium methoxide

W = Weight of the sample

N = Normality of methoxide

EW = Equivalent weight factor

- 2) **Determination of the Concentration Expressions:** For example, Isoprenaline solutions are mixed with glacial acetic acid and titrated with 0.1N perchloric acid using crystal violet as indicator.

1ml of 0.1N perchloric acid \equiv 0.5206gm of isoprenaline

- 3) **Determination of Hydrophobic Compounds:** Amantidine HCl barbiturates alkaloids.

- 4) **Determination of Phenobarbitone:** 0.1gm of sample is dissolved in 5ml of pyridine, 0.25ml of thymolphthalein solution, and 10ml of silver nitrate-pyridine reagent. The resulting solution is titrated with 0.1M ethanolic NaOH until blue colour is attained. Simultaneously a blank is carried out.

1ml of 0.1M ethanolic NaOH \equiv 0.01161gm of phenobarbital

- 5) **Determination of Diuretics:** Small quantity of the drug is dissolved in anhydrous pyridine which is heated and then cooled. The resulting solution is titrated with 0.1M of tetrabutyl ammonium hydroxide solution. 1ml of 0.1M tetrabutylammonium hydroxide \equiv 0.01161gm of hydrochlorthiazide

- 6) **Determination of the Steroids:** Sample solution (e.g., methyl sterone, tetrahydrosteroid, estradiol, etc.) is mixed with 2ml of dimethylformamide and 25ml of chloroform. To 5ml of resultant solution, 2 drops of thymol blue indicator solution is added and titrated with methanolic potassium hydroxide solution. Simultaneously blank is carried out.

- 7) **Determination of Anti-tubercular Drugs:** 0.2gm of drug is dissolved in a mixture of 100ml of acetic acid and 5ml of mercuric acetate solution. The resultant solution is titrated with 0.1M perchloric acid (HClO_4) using crystal violet as indicator.

1ml 0.1M HClO_4 \equiv 0.01386gm of ethambutol

- 8) **Determination of Adrenergic Drugs:** Drug solutions are mixed with glacial acetic acid and titrated with 0.1N perchloric acid using crystal violet as an indicator.

1ml of 0.1N perchloric acid \equiv 0.5206gm of isoprenaline
 \equiv 0.3193gm of noradrenaline
 \equiv 0.05767gm of salbutamol
 \equiv 28.08gm of xylometazoline