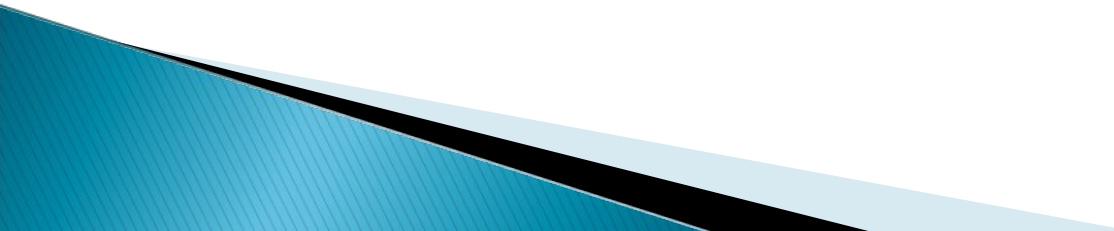


# Non aqueous titration

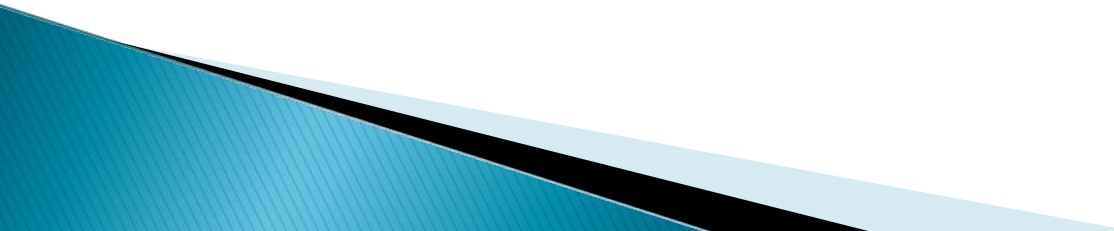
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# NONAQUEOUS ACID–BASE TITRATION.

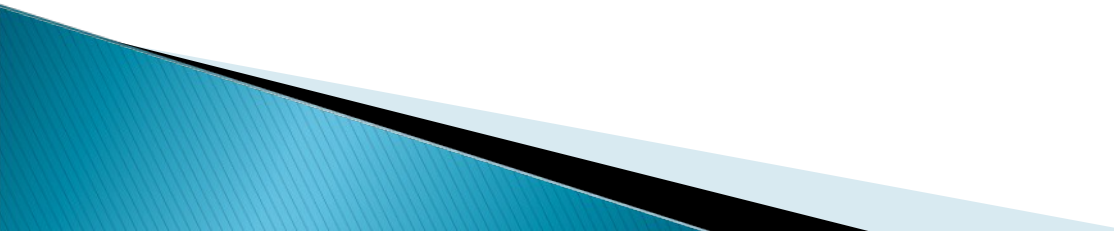
**Titration in water solutions is limited by factors:**

- ▶ **It is impossible** to titrate for a mix of acids or the bases
  - ▶ **It is impossible** to titrate for a mix of strong and weak acids (bases)
  - ▶ **It is impossible** to titrate separately for a mix of acids (bases) with near constants of dissociation
  - ▶ **It is impossible** to define substances which are insoluble in water.
- 

## Non-aqueous titrations have the following advantages

- ▶ Organic acids and bases that are insoluble in water are soluble in non-aqueous solvent.
  - ▶ A non-aqueous solvent may help two or more acids in mixture. The individual acid can give separate end point in different solvent.
  - ▶ Enlargement of solubility range: many substances that are not soluble in water can be easily titrated in water-free media (e.g. fats and oils)
  - ▶ Enlargement of application range: weak bases and acids can be easily titrated
  - ▶ Substance compositions that cannot be separately determined in aqueous media can often be titrated in non-aqueous media
  - ▶ Non-aqueous solvents are useful for the titration of very weak acids or bases that cannot be titrated in water
  - ▶ Non aqueous titrations are simple and accurate, examples of non aqueous titration are :
  - ▶ Ephedrine preparations, codeine phosphate in APC, tetracycline, teramycin, Anti- histamines and various piprazine preparations.
- 

# What is non-aqueous solvent & it's types

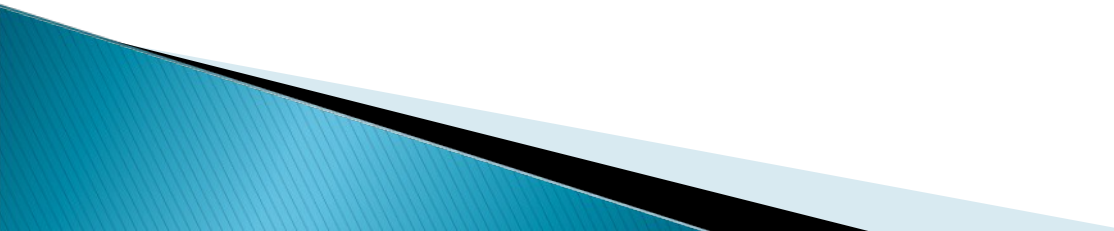
- Solvent which are used in non aqueous titration are called non aqueous solvent.
  - They are following types:-
    1. Aprotic Solvent
    2. Protogenic Solvent
    3. Protophillic Solvent
    4. Amphiprotic Solvent
- 

# 1. Aprotic solvent

- Aprotic solvent are most important solvent in this titration. This solvent are chemically inert and they work as a catalyst. Like this solvent are increase the rate of speed in reaction and also decrease the rate of speed in reaction during the chemical process or reaction it will depend on condition.

- Neither acidic nor basic (inert solvent),

The most important examples of aprotic solvent are

- Chloroform
  - Benzene
- 

## 2. Protogenic solvent

- ▶ Protogenic solvent are acidic in nature. And they can donate the proton, and they enhance the strength of weak bases.

Examples of Protogenic solvent are

- ▶ HCL
- ▶  $\text{H}_2\text{SO}_4$

### 3. Protophilic solvent

- ▶ Protophilic solvents are basic in nature. Which possess a high affinity for protons.

Examples:- Liquid ammonia, amines and ketones.

## 4. Amphoteric Solvent

- ▶ Amphoteric solvents are those solvents that work as both protogenic or protophilic. It means amphoteric solvents are acidic and basic in nature. And they accept the proton and donate the proton.

For examples:- Water, Alcohols and weak organic acids



## Detection of end point

- Visual indicators are formed to the most suitable for the detection of end point in non-aqueous titration.
- The important indicators used for non-aqueous titration are follow:-
  1. Crystal violet:- It is used as 0.5% solution in glacial acetic acid, it gives violet colour in basic medium and yellowish green in acidic medium.
  - It is most widely used for the titration of pyridine with perchloric acid.
  2. Oracet Blue B Indicator:- It is prepared 0.5% glacial acetic acid. It gives blue colour in basic medium while pink colour in acidic medium.

# Selection of Solvents for NAT

Acetic acid used for titration of weak bases,  
Nitrogen containing compounds

Acetonitrile / with ACOH: Metal ethanoates

Alcohols (IPA, nBA) : Soaps and salts of organic  
acids,

DMF: Benzoic acid, amides etc



# Titrants for NAT

- ▶ Perchloric acid in acetic acid
  - Amines, amine salts, amino acids, salts of acids
- ▶ Potassium Methoxide in Toluene-Methanol
- ▶ Quan ammonium hydroxide in Acetonitrile-pyridine
  - Acids, enols, imides & sulphonamides

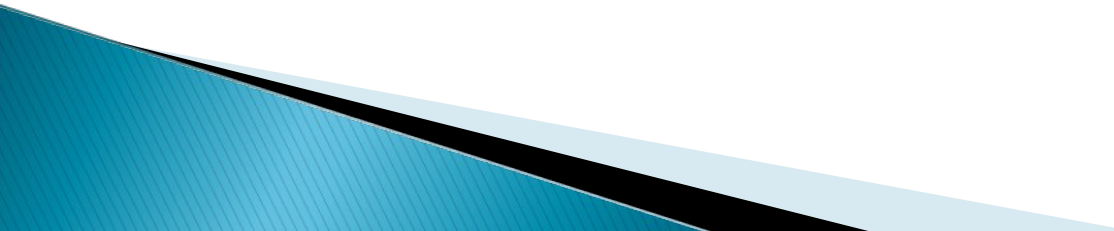
# ASSAY BY NON-AQUEOUS TITRATIONS

- ▶ **Acidimetry in Non-aqueous Titrations**—It can be further sub-divided into *two* heads, namely :
  - (i) Titration of primary, secondary and tertiary amines, and
  - (ii) Titration of halogen acid salts of bases.
- ▶ **Alkalimetry in Non-aqueous Titrations**—titration of acidic substances

# ACIDIMETRY IN NON AQUEOUS TITRATIONS

**Example : Primary amines**

**METHODOLOGY:** four steps

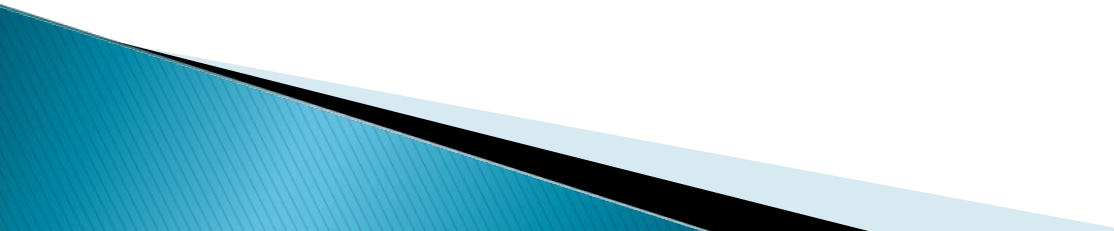
- ▶ (i) Preparation of 0.1 N Perchloric acid,
  - ▶ (ii) Standardization of 0.1 N Perchloric Acid,
  - ▶ (iii) Choice of Indicators, and
  - ▶ (iv) Effect of Temperature on Assays
- 

# PREPARATION OF 0.1 N PERCHLORIC ACID

- ▶ **Materials Required** : 8.5 ml of perchloric acid (70.0 to 72.0%) ; 1 Litre of glacial acetic acid ; 30ml of acetic anhydride.
- ▶ **Procedure** : Gradually mix 8.5 ml of perchloric acid to 900 ml of glacial acetic acid with vigorous and continuous stirring. Now add 30 ml acetic anhydride and make up the volume to 1 litre with glacialacetic acid and allow to stand for 24 hours before use.
- ▶ The acetic anhydride reacts with the water (approx. 30%) in perchloric acid and some traces in glacialacetic acid thereby making the resulting mixture practically anhydrous. Thus, we have :



# STANDARDIZATION OF 0.1 N PERCHLORIC ACID

- ▶ 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.
- 

# CHOICE OF INDICATORS

S.No.	Name of Indicator	Colorchange	Observed	Acidic
		Basic	Neutral	
1	Crystal violet (0.5% w/v in glacial acetic acid)	Violet	Bluish green	Yellowish green
2	Oracet Blue B(0.5% in glacial acetic acid)	Blue	Purple	Pink
3	$\alpha$ -Naphtholbenzein (0.2% in glacial acetic acid)	Blue	Orange	Dark-green
4	Quinalidine Red (0.1% in methanol)	Magenta	—	Almost colourless



# PRECAUTIONS

(a) Perchloric acid is usually available as a 70 to 72% mixture with water. It usually undergoes a spontaneous explosive decomposition and, therefore, it is available always in the form of a solution.

(b) Conversion of acetic anhydride to acetic acid requires 40-45 minutes for its completion. It being an exothermic reaction, the solution must be allowed to cool to room temperature before adding glacial acetic acid to volume,

(c) Avoid adding an excess of acetic anhydride especially when primary and secondary amines are to be assayed, because these may be converted rapidly to their corresponding acetylated non-basic products :



(d) Perchloric acid is not only a powerful oxidising agent but also a strong acid. Hence, it must be handled very carefully.

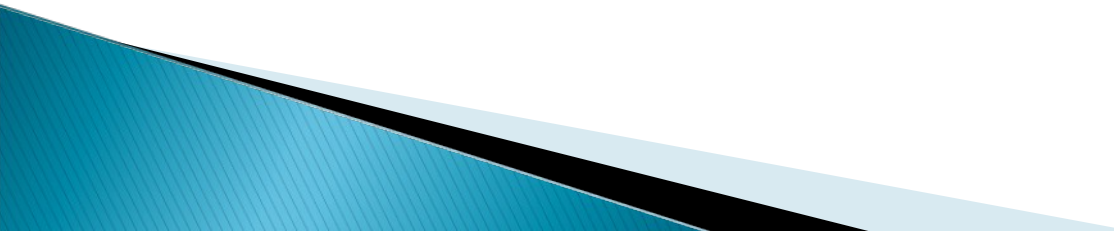
# OTHER EXAMPLES

S.No.	Name of Substance	Indicator Employed
1	Amantadine hydrochloride	Crystal violet
2	Chlorpromazine hydrochloride	Methyl orange
3	Clonidine hydrochloride	$\alpha$ -Naphthol benzein
4	Cyproheptadiene.HCl	Crystal violet
5	Ephedrinehydrochloride	-do-

## **Preparation of 0.1 N 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.



### **Preparation of 0.1 N Sodium Methoxide**

It is prepared exactly in a similar manner as for 0.1 N Potassium Methoxide, using 2.3 g of freshly-cut sodium in place of potassium.

### **Preparation of 0.1 N Lithium Methoxide**

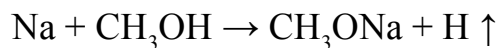
It is prepared as for 0.1 N Potassium Methoxide, but using 0.7 g of lithium in place of potassium.

### **Standardization of 0.1 N Methoxide Solution**

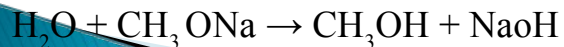
**Materials Required:** Dimethylformamide (DMF) : 10 ml ; Thymol blue (0.3% in MeOH) ; 0.1 N lithium methoxide in toluene methanol ; benzoic acid : 0.6 g.

**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 N lithium Methoxide in toluene-methanol. Quickly introduce 0.06 g of benzoic acid and titrate immediately with Methoxide in toluene methanol.

**Caution: Care must be taken to avoid contamination of neutralized liquid with atmospheric carbon dioxide.**



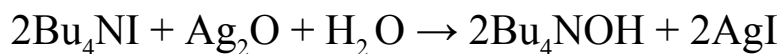
Interaction between sodium metal and methanol is an exothermic reaction and hence, special care must be taken while adding the metal into the dry solvent in small lots at intervals with adequate cooling so as to keep the reaction well under control.



## **Preparation of 0.1 N Tetrabutylammonium Hydroxide in Toluene-Methanol**

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

**Procedure:** Carefully dissolve 40 g of tetrabutylammonium iodide (Bu<sub>4</sub>NI) in 90 ml of absolute methanol, add to it 20 g of finely powdered purified silver oxide and finally shake the mixture thoroughly for 1 hour. Centrifuge about 2-3 ml of the resultant mixture and test for iodide in the supernatant liquid. In case, it gives a positive test, add about 2 g more of silver oxide and shake for an additional period of 30 minutes. The said method may be repeated until the supernatant liquid obtained is completely free from iodide. The mixture thus obtained is filtered through a fine sintered glass filter and finally rinse the container with 3 portions, each of 50 ml of dry toluene. These washings may be added to the filtrate and the final volume is made up to 1 litre with dry toluene. The clear solution may be flushed with CO<sub>2</sub>-free nitrogen for at least five minutes and duly protected from both CO<sub>2</sub> and moisture during storage.



Tetrabutyl-  
ammonium iodide

Tetrabutyl ammonium  
hydroxide

## **Standardization of 0.1 N Tetrabutylammonium Hydroxide**

**Materials Required :** Benzoic acid : 60 mg ; dimethylbromide : 10 ml ; thymol blue solution (0.3% w/v in methanol) ; 0.1 N 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 N tetrabutylammonium hydroxide. Allow the benzoic acid to dissolve gradually and completely and titrate with 0.1 N tetrabutylammonium hydroxide.

0.01221 g  $\text{C}_7\text{H}_6\text{O}_2 \equiv 1 \text{ ml of } 0.1 \text{ N}$

