

Acidimetry in Non-Aqueous Titrations

In order to perform feasible titrations of weak bases, the solvent system should be selected specifically in such a fashion so as to eliminate as far as possible the competing reaction of water for the proton besides enhancing the strength of the basic species.

Titration of Weak Bases by Non Aqueous Titration

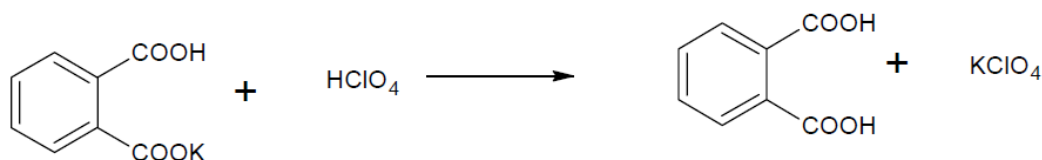
Following points should be considered: -

1. Titrant used.
2. Preparation of 0.1N (HClO_4) and its standardization.
3. Solvent used.
4. Practical examples of weak bases along with indicators.
5. Typical example of assay of weakly basic substance e.g. ephedrine .

Titrant used: Solution of HClO_4 in either glacial acetic acid or dioxane solution is used for titration of weak bases. Generally HClO_4 with a normality of 0.1N to 0.05N is used.

Preparation of 0.1N solution of HClO_4 and its standardization: Dissolve 8.5 ml of 72% HClO_4 in about 900 ml glacial acetic acid with constant stirring, add about 30 ml acetic anhydride and make up the volume (1000 ml) with glacial acetic acid and keep the mixture for 24 hour. Acetic anhydride absorbed all the water from HClO_4 and glacial acetic acid and renders the solution virtually anhydrous. HClO_4 must be well diluted with glacial acetic acid before adding acetic anhydride because reaction between HClO_4 and acetic anhydride is explosive.

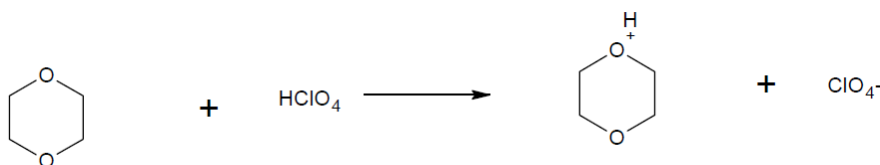
1. Standardization of the above prepared 0.1N HClO_4 with A.R. Grade Potassium acid Phthalate.



1 ml of 0.1N HClO_4 = 0.020414 gms of potassium acid Phthalate.

To 500 mg of potassium acid phthalate add 25 ml of glacial acetic acid and add few drops of 5% w/v crystal violet in glacial acetic acid as indicator. This solution is titrated with 0.1 HClO_4 . The colour changes from blue to blue green.

2. Solution in HClO_4 in dioxane may be the 2nd titrant, which could be used. It is standardize in the same manner as acetous perchloric acid. High quality dioxane must be used otherwise titrant will become dark. Dioxane can be purified by passing resin or by shaking it with asbestos and then filter it.

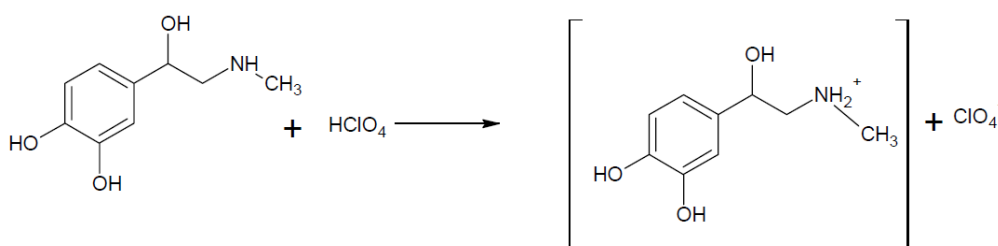
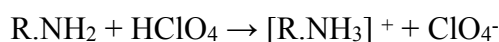


Solvent used : Glacial acetic acid alone or sometimes in combination with some aprotic solvents is often used. The other solvents are CHCl_3 , benzene, chloro benzene, acetic anhydride and various combinations of these sometime glycohydrocarbon mixtures are also used.

Indicators used: Crystal violet 0.05% w/v in glacial acetic acid, methyl red 0.1% w/v in anhydrous methanol, oracet blue 0.5% w/v in glacial acetic acid.

Practical Examples of Weak Bases: It includes adrenaline acid tartarate, erythromycin strerate, metronidazol tartrate methyl dopa, noradrenaline, orphenadrine citrate, prochlorperazine maleate etc.

Asssay of Adrenaline: In general, the reaction-taking place between a primary amine and perchloric acid may be expressed as follows:



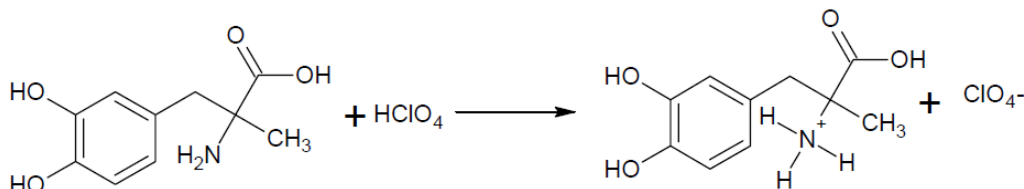
Hence, 183.2 g of $\text{C}_9\text{H}_{13}\text{NO}_3 \equiv \text{HClO}_4 \equiv \text{H} \equiv 1000 \text{ ml N}$ or 0.01832 g of $\text{C}_9\text{H}_{13}\text{NO}_3 \equiv 1 \text{ ml}$ of 0.1 N HClO_4

Procedure: Weigh accurately about 0.3 g of sample into a 250 ml conical flask; add Glacial acetic acid (50 ml), warm gently, if necessary. Cool and titrate with 0.1 N perchloric acid using crystal violet or oracet blue B as indicator.

Calculations: The percentage of adrenaline present in the sample is given by:

$$\% \text{Adrenaline} = \frac{\text{X ml} \times \text{Normality (Calculated)} \times 0.01832 \times 100}{\text{N(Given)} \times \text{Wt. of sample(in gm)}}$$

Assay of Methyldopa: The specific reaction between methyldopa and perchloric acid is expressed by the



following equation:

Hence, 211.24 g of $\text{C}_{10}\text{H}_{13}\text{NO}_4 \equiv \text{HClO}_4 \equiv \text{H} \equiv 1000 \text{ ml N}$ Or 0.02112 g of $\text{C}_{10}\text{H}_{13}\text{NO}_4 \equiv 1 \text{ ml}$ of 0.1 N HClO_4

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

Procedure: Weigh accurately about 0.2 g of sample and dissolve in a mixture of 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 N perchloric acid. Perform a blank determination and make any necessary correction. Each ml of 0.1 N perchloric acid is equivalent to 0.02112 g of $C_{10}H_{13}NO_4$.

Calculations: The percentage of methyldopa present in the sample is given by :

$$\% \text{Methyldopa} = \frac{X \text{ ml} \times \text{Normality (Calculated)} \times 0.02112 \times 100}{N(\text{Given}) \times \text{Wt. of sample(in gm)}}$$

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: anhydride, acids, amino acids, acid halides, enols (viz., barbiturates), xanthenes, 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.

Preparation of 0.1 N Potassium Methoxide in Toluene-Methanol:

Material Required: Absolute methanol, dry toluene, Potassium metal.

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 (5.6 gm) 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 2.3g 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

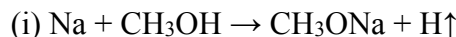
Material Required: Dimethylformamide (DMF): 10 ml; thymol blue (0.3% in MeOH); 0.1 N lithium methoxide in toluene methanol; benzoic acid: 0.6 g.

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

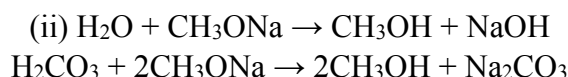
toluene-methanol. Quickly introduce 0.06g of benzoic acid and titrate immediately with methoxide in toluene-methanol.

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

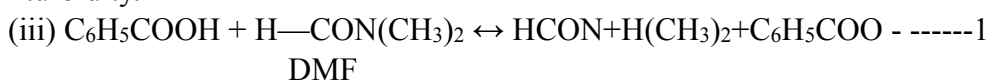
Equations: The various equations involved in the above operations are summarized as stated below:



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.



The clear solution of sodium methoxide must be kept away from moisture and atmospheric CO₂ as far as possible so as to avoid the above two chemical reactions that might ultimately result into the formation of turbidity.



Summing up: $\text{C}_6\text{H}_5\text{COOH} + \text{CH}_3\text{ONa} \rightarrow \text{C}_6\text{H}_5\text{COONa} + \text{CH}_3\text{OH}$

Step 1: It shows the solution of benzoic acid (primary standard) in DMF,

Step 2: It depicts ionization of sodium methoxide,

Step 3: It illustrates the interaction between the solvated proton and the methylated ion.

In summing up, the net reaction between the water in the solvent (DMF) and the titrant is equivalent to the volume of sodium methoxide consumed by DMF or may be considered as a blank determination.

N/10 KOH in Methanol

Dissolve 5.6 gm of anhydrous KOH in 1000 ml of anhydrous methanol. This titrant is not as powerful as others. Its main disadvantage is that it reacts with acidic functional groups and produces a molecule of water, which would affect the sensitivity of titration.

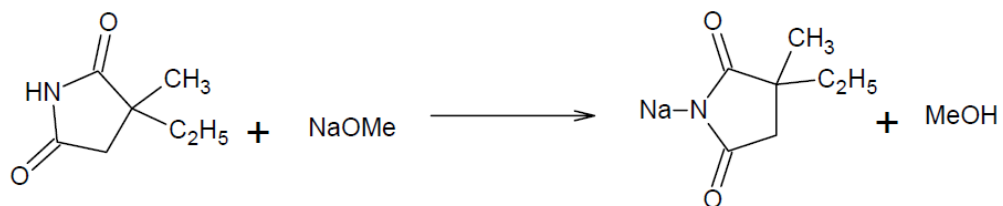
Standardisation : All these titrants are usually standardized against standard benzoic acid AR-Grade. A sufficient amount of benzoic acid which would give a titrate value of 20-30 ml is transferred in a dry flask and dissolved in 25 ml dimethylformamide, 2-3 drops of 0.5% thymol blue indicator in dry methanol is added to the solution. A blank titration is also performed in the solvent to account acidic impurity in dimethylformamide and the correction is made accordingly.

Assay of Ethosuximide

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

Procedure: Weigh accurately about 0.2 g of the sample, dissolve in 50 ml of dimethylformamide, add 2 drops of azo-violet solution and titrate with 0.1 N sodium methoxide to a deep blue end point, taking precautions to prevent absorption of atmospheric carbon dioxide. Perform a blank determination and make any necessary correction.

Each ml of 0.1 N sodium methoxide is equivalent to 0.01412 g of C₇H₁₁NO₂.

Equations:**Calculations:**

Therefore, 141.17 g C₇H₁₁NO₂ \equiv NaOMe \equiv H \equiv 1000 ml N0.01417 g C₇H₁₁NO₂ \equiv 1 ml 0.1 N NaOMe