Pharmaceutical Analytical Chemistry I

الأستاذ الدكتور جمعه الزهوري (دكتوراه صيدلة-ألمانيا 1991)

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Non aqueous Neutralization Titration

Acid-Base Titrations in Non-aqueous Solvents

Water is a common solvent for conducting acid-base titrations.

It is not the only solvent that can be used.

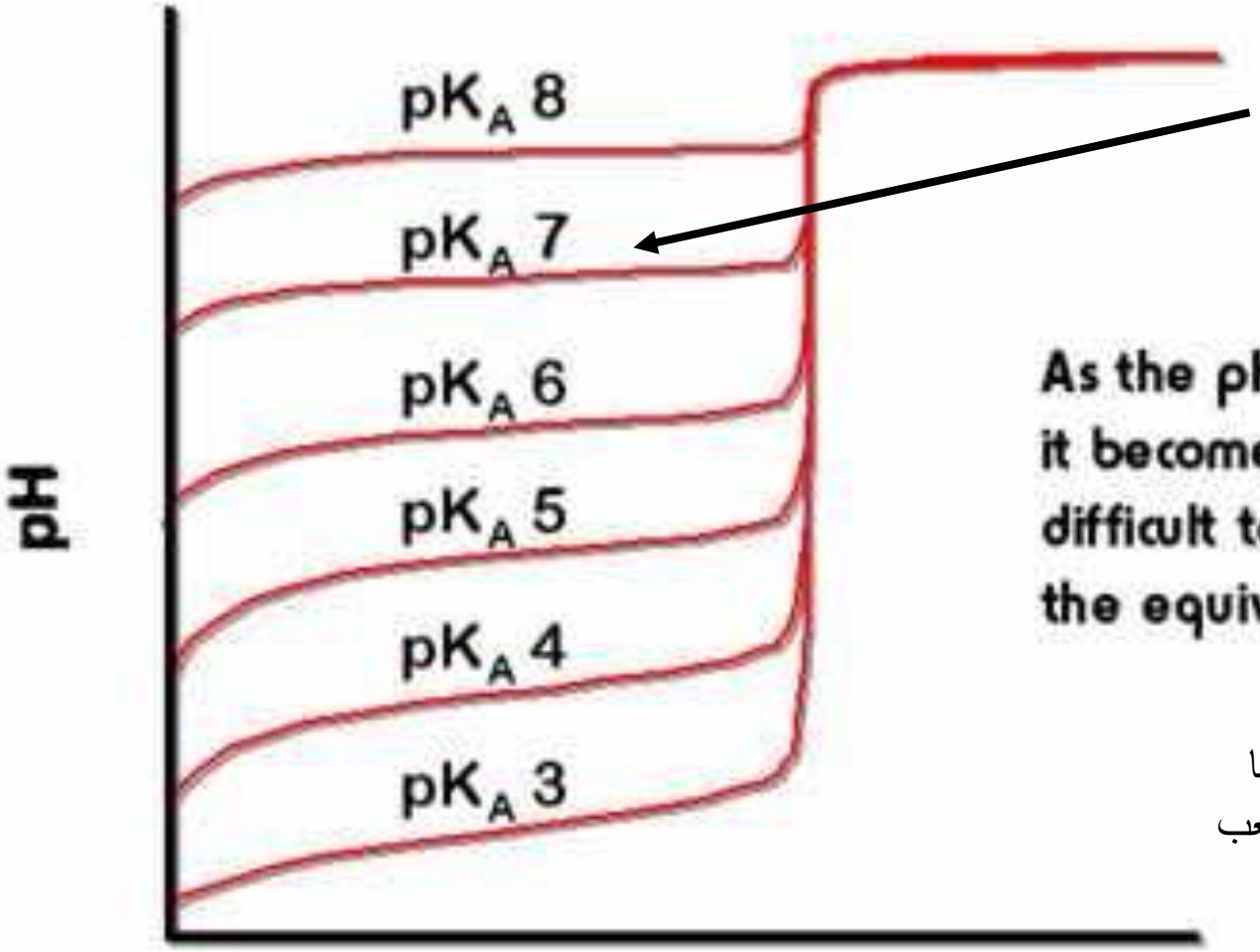
One reason for using a different solvent is solubility. You must be able to dissolve you sample for reliable titration results.

Example. Many organic acids will dissolve more readily in methanol

الماء هو المحل الشائع ولكنه ليس الوحيد ، فكثير من المواد لاتنحل بالماء مثل بعض الحموض العضوية

Prof. J. Al-Zehouri

Why use non-aqueous solvents?



As the pK_A increases, it becomes more difficult to detect the equivalence point.

كلما زادت قيمة ال pKa كلما
اصبح تحديد نقطة التكافؤ صعب

Why use non-aqueous solvents?

When the K_A of a weak acid is $< 10^{-7}$

The basicity of A^- is high enough reconvert it to HA.

This reduces the % neutralization well below what is expected for a quantitative neutralization (99.9%)

The same is true for very weak bases.

عندما يكون الحمض ضعيفاً فإن الشاردة السالبة تعود لتشكل HA مما يجعل التفاعل غير كمي

GENERAL RULE

Acids with pKa > 7 or bases with pKa < 7 cannot be determined accurately in aqueous solution

Non-aqueous solvents

Different solvents can affect a titration curve. Proper selection can result in an easier to detect endpoint.

Three types of solvents

Amphiprotic

Non-ionizable with basic properties

Aprotic or inert

Aprotic

- **Aprotic**, those that are neither appreciably acidic nor basic , the “ inert” solvent , such as benzene and carbon tetrachloride.

لا تملك صفات حمضية ولا اساسية مثل البنزن ورابع كلور الفحم

Non-aqueous solvents

Aprotic or inert solvents

There is no interaction with the acid or base. They simply serve to provide a medium in which the sample species or titrant are soluble.

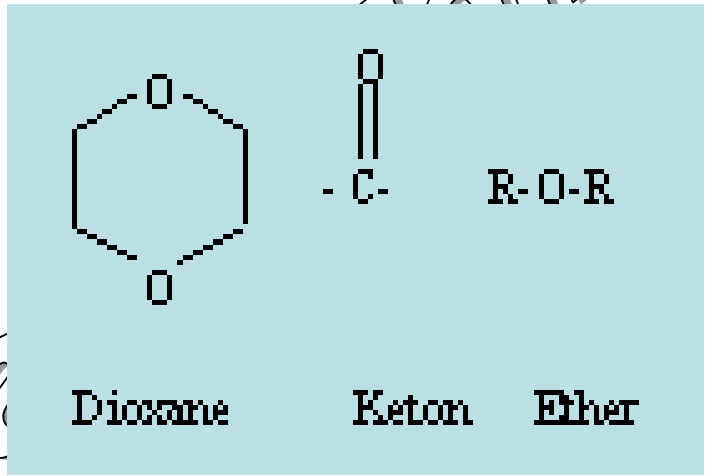
Example

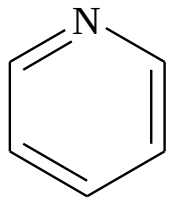
$$CCl_4 + HA \longrightarrow CCl_4 + HA_{(s)}$$

المذيبات الخاملة لا تتفاعل لا مع الحمض ولا
مع الأساس ولكن تؤمن وسط لانحلال المادة

Basic but not acidic

- **Basic but not acidic** – nonionizable - for example , ether ,dioxane, ketones ,and pyridine.
- Most of these are extremely weak bases. There are no known examples of solvents that are acidic but not basic





Pyridine

تملك صفة اساسية جانحة ولكنها لا تتأين

ولا يوجد مواد بصفة حمضية جانحة لاتتأين

Non-aqueous solvents

Non-ionizable with basic properties

No autoprotolysis but the solvent has a group that can react with acids. No reaction with bases.

Examples

Pyridine

$$C_5H_5N + HA \longrightarrow C_5H_5NH^+ + A^-$$

Ethers

$$R_2O + HA \longrightarrow R_2OH^+ + A^-$$

Amphiprotic

- **Amphiprotic**, those which posses both acidic and basic properties , such as water , ethanol , and methanol.
- These are **ionizable** solvents.

Non-aqueous solvents

المذيب يلعب دوراً يعتد به بالمعايرات اللامائية

With amphiprotic solvents, the solvent plays a significant role in determining the observed acid-base chemistry and titration curves.

Non-ionizing solvents only act to transport on pairs.

Aprotic solvents only contribute solubility.

We'll now look as several amphiprotic solvents.

Non-aqueous solvents

Amphiprotic examples

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

$$2\ CH_3OH \rightleftharpoons CH_3OH_2^+ + CH_3O^-$$

$$2\ CH_3COOH \rightleftharpoons CH_3COOH_2^+ + CH_3OO^-$$

$$2\ NH_3 \rightleftharpoons NH_4^+ + NH_2^-$$

In each case, the solvent dissociates such that you get SH_2^+ and S^-

$$K_S = [\ SH_2^+\ ]\ [\ S^-\ ]$$

Also Amphiprotic solvents undergo self-ionization ,or **autoprotolysis** while Ks = **autoprotolysis constant**

Titration of *weak base* in nonaqueous solvents

Water

Regardless of the type of acid, each produce H_3O^+ even if they are are of different strength.

The actual acid strength is actually determined by the strength of H_3O^+

This is referred to as the **leveling effect**.

The same effect holds for bases based on variations in $[OH^-]$.

Water

So H_3O^+ is the only aqueous acid and OH- is the only aqueous base.

Our acids and bases can't be any stronger than these species.

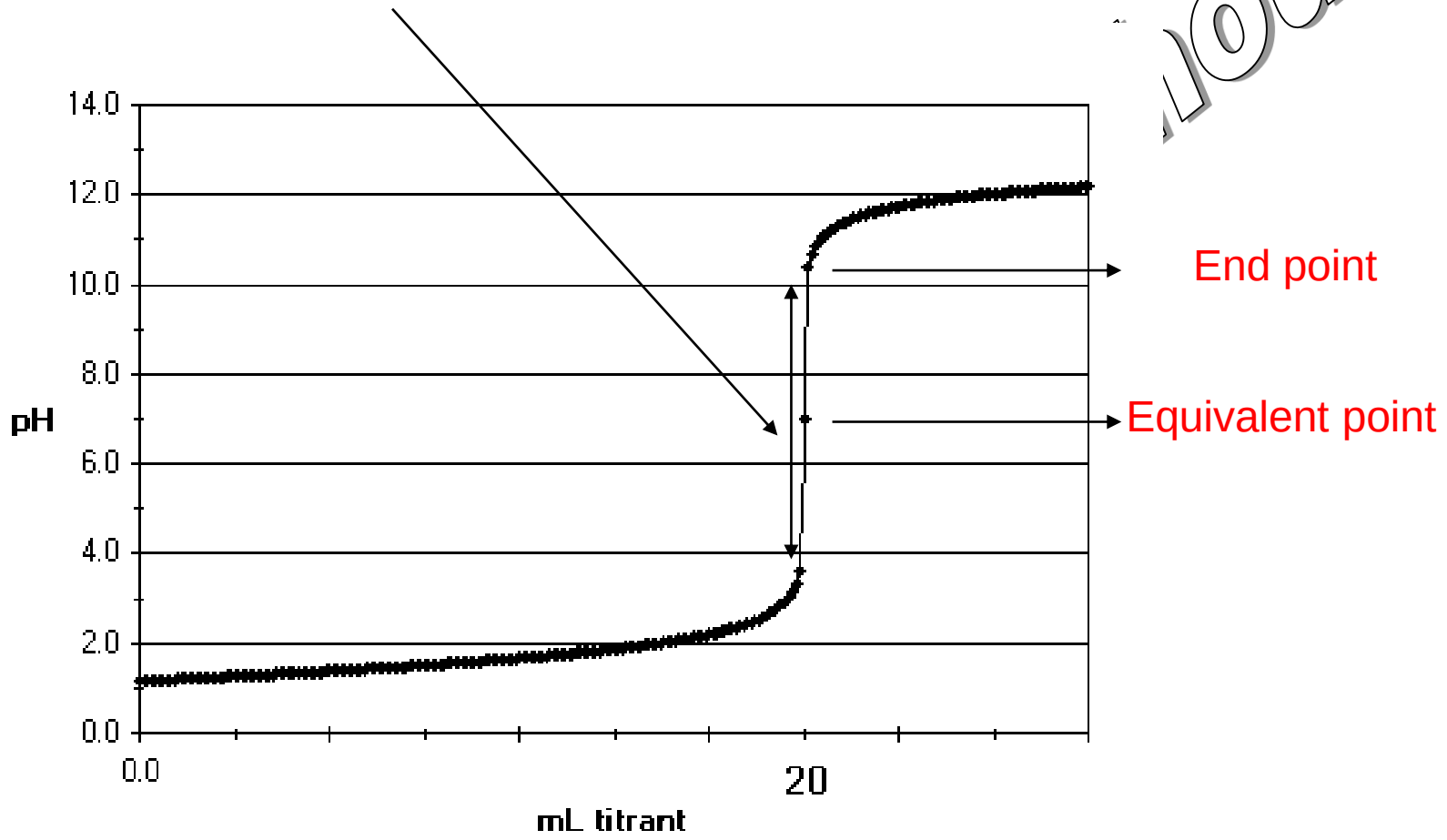
Weak acids and bases have as an additional limit incomplete ionization.

It makes sense that many of our strong acids are significantly different – why would they be of the same strength?

Leveling effect of water

- The mineral acids $HClO_4$,HCl and HNO_3 all transfer their protons completely to water (due to the relative basicity of water) and are leveled to the same strength in water.
- This is so even though Perchloric acid is inherently a stronger acid than the others.
- The phenomenon is called the **leveling effect**.
- Acids that are leveled to the same strength cannot be differentiated.

الماء يستطيع استقبال كافة البروتنات



Titration curves for strong acid (20 ml HCl 0.1N with strong base (NaOH 0.1 N)

Acetic acid

- In glacial acetic acid ,the strongest acid that can exist H_2OAC^+ , but the mineral acids are not completely ionized in this acidic solvent and their strengths can be differentiated.
- On the other hand , acetic acid is stronger leveling solvent than water for **Bases**

Acetic acid

amphiprotic solvent

$$2\ CH_3COOH \rightleftharpoons CH_3COOH_2^{+} + CH_3OO^{-}$$

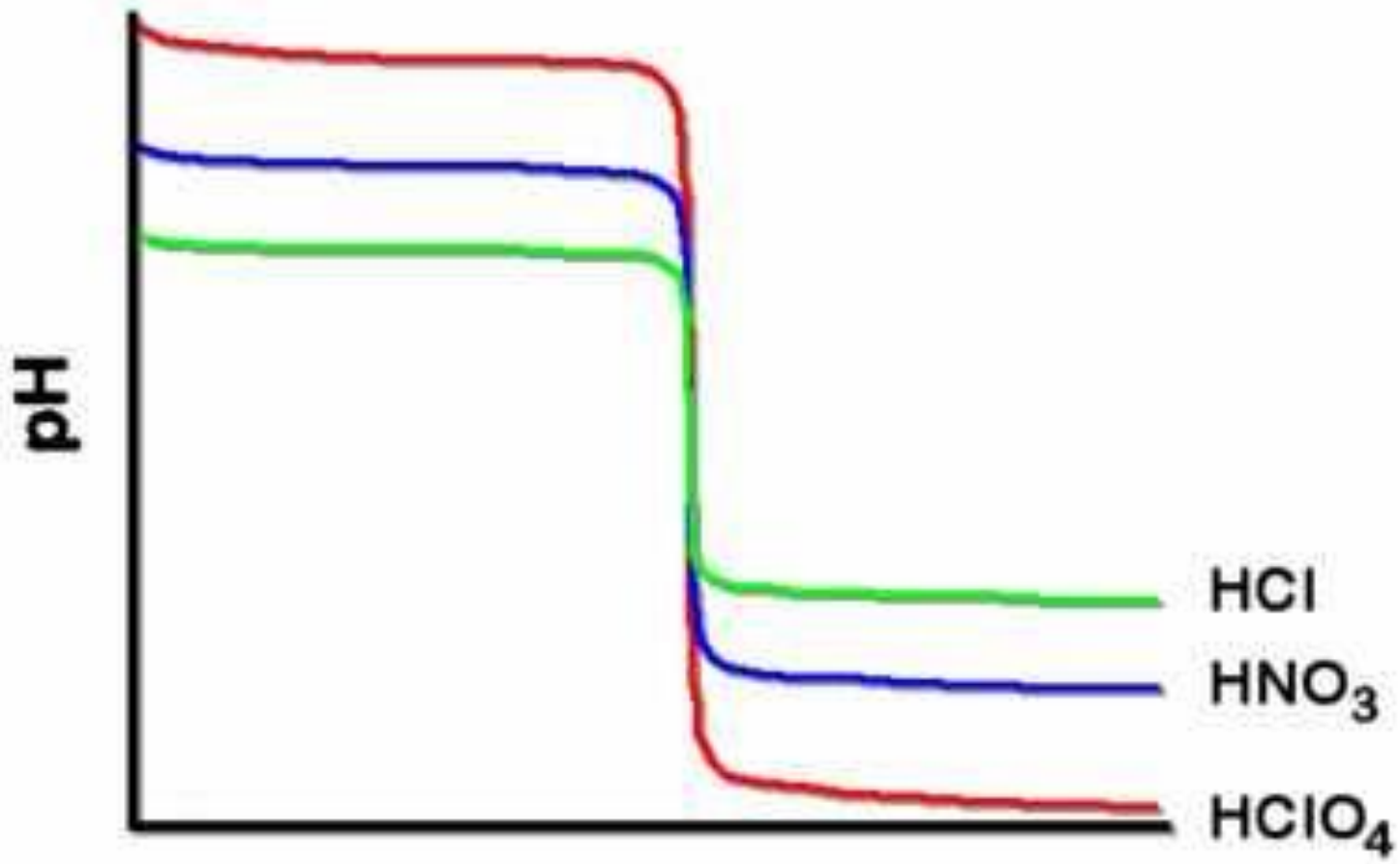
Acetic acid

Since acetic acid is less basic than water, it does not level strong acids.

This increases the number of acids and bases we can titrate.

Acetic still levels aliphatic amines and simple aromatic amines.

Perchloric acid



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Perchloric acid

This is the most common acid to use in non-basic solvents (like acetic acid)

It also serves as an excellent example of what is possible when using a solvent other than water.

While perchloric acid is more hazardous than other acids, in acetic acid, it produces the sharpest endpoint.

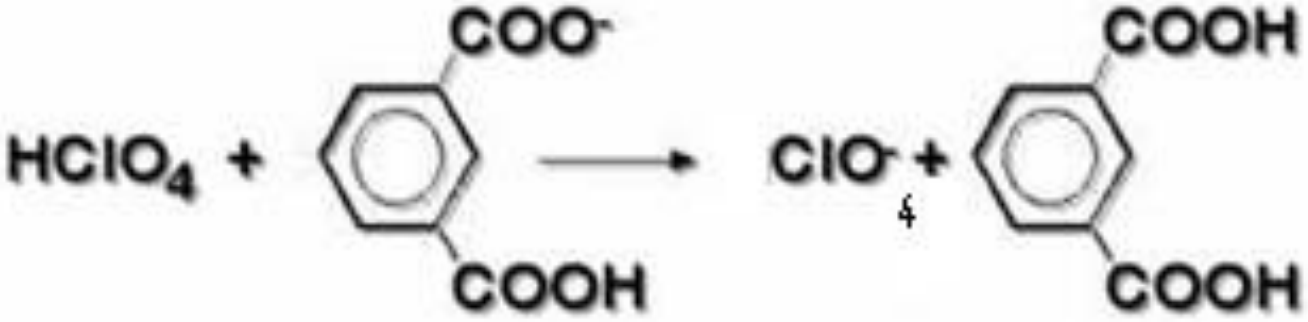
Hazardous=
Danger

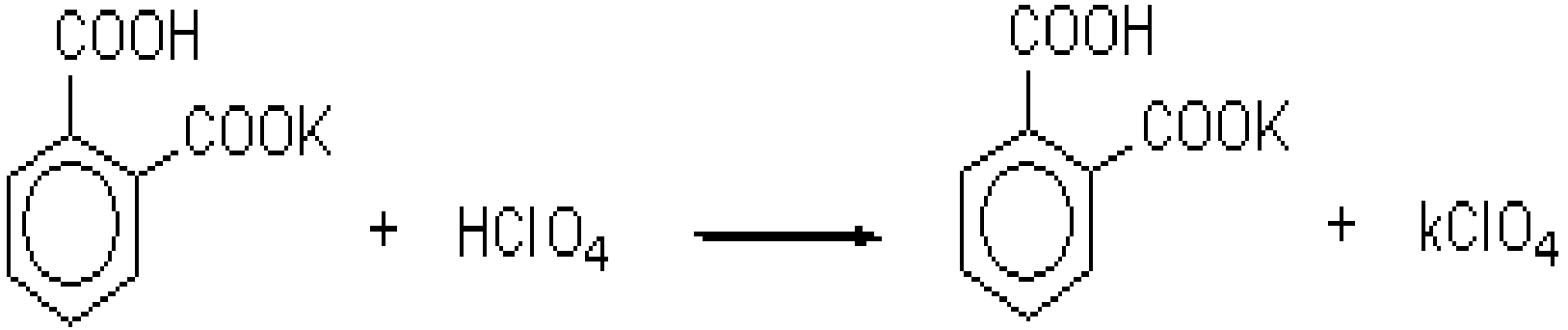
Perchloric acid

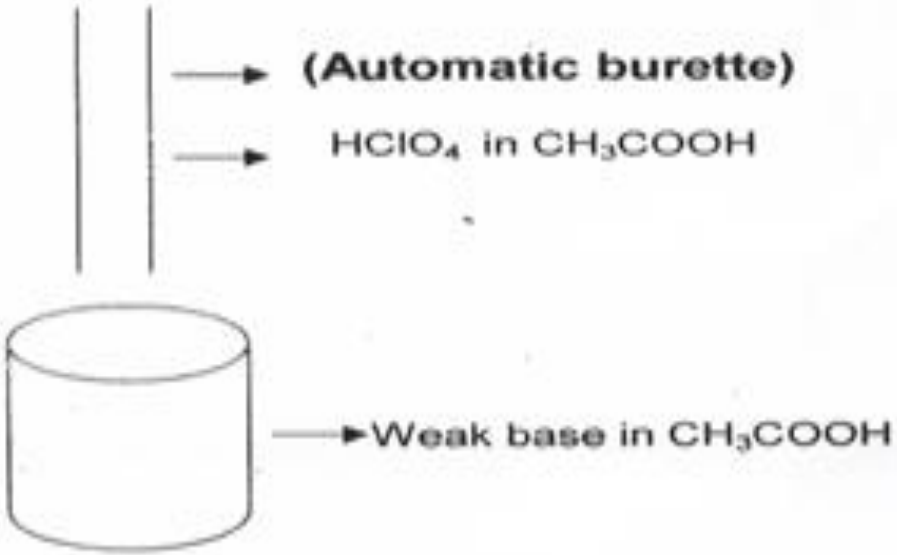
Preparation of standard perchloric acid

Typically use 0.01 to 0.5 M solutions initially prepared by dilution of 70% perchloric acid in glacial acetic acid.

KHP is used as a primary standard but as a base - must heat solution to dissolve KHP.







* Burette : $HClO_4 + CH_3COOH \longrightarrow CH_3COOH_2^{\oplus} + ClO_4^{\ominus}$
Acétacetium ion

* Conical : $R_1R_2N: + CH_3COOH \rightarrow R_1R_2N^{\oplus}H + CH_3COO^{\ominus}$ (Acetate ion)

* Reaction : $CH_3COOH_2^{\oplus} + CH_3COO^{\ominus} \longrightarrow 2CH_3COOH$

* Indicato: $IND + CH_3COOH_2^{\oplus}ClO_4^{\ominus} \rightleftharpoons IND^{\oplus}ClO_4^{\ominus} + CH_3COOH$

Crystal Violet
Naphtolbenzein
Malachite Green

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Titration of halides *weak base* in nonaqueous solvents

Chloride and Bromide salt

Titration of haloids weak base in nonaqueous solvents

- When the base in the form of a salt of aweak acid, removal an anionic counter ion prior to titration is not necessary , e.g. tartarate, acetate or succinate.
- When abase in the form of salt of chloride or bromide ,The counter ion has to be removed prior to titration. This achieved by addition of mercuric acetate $Hg(CH_3COO)_2$

$$2\ R_3NH^+\ Hal^- + Hg(OAC)_2 \longrightarrow$$

$$2R_3NH^+.2OAC^- + HgHal_2$$

Titration

of *weak acid* in

nonaqueous solvents

Titration of weak acid in nonaqueous

- -SH , -SO_2 (Sulphathiazole, Phenobarbital..
- The most common standard solution: Lithium or Sodium methoxide in MeOH or Tetrabutylamoniumhydroxide (TBAH) in DMF ,
- The most comment nonaqueous solvent:

  DMF , Butyl amine ,Pyridine
- Indicators (Thymole blue , Brome thymolblue,

Alkali metal bases

Methoxides

These are even stronger bases but decompose in water.

They are prepared by adding sodium metal to methanol.

$$2\ Na_{(s)} + 2\ MeOH \longrightarrow 2\ NaMeO + H_{2(g)}$$

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Titrations in nonaqueous solvents

Pharmaceutical applications

1. Titration of Drugs with basic characters.
2. Titration of Drugs with acidic characters.

Titration of Drugs with basic characters.

Non-aqueous titration with acetous perchloric acid is used in the pharmacopeias assays of :

- Adrenaline
- Metronidazole
- Codeine
- Chlorhexidine acetate
- Chlorpromazine HCl
- Amitriptyline HCl
- Propranolol HCl
- LidocainHCl

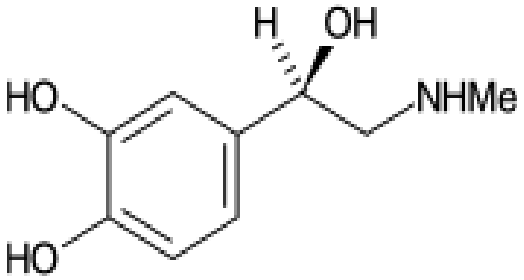
And quaternary amine salts such as : للوهن العضلي

- Neostigmine bromide
- Pancuronium bromide

مرخي عضلي

منبه بيتا بحالات الريو ويثبط انتاج الخلط المائي بحالات ارتفاع ضغط العين

Adrenaline / Epinephrine



183.2 $C_9H_{13}NO_3$

Action and use

Beta- adrenoceptor agonist; used in treatment of glaucoma.

Assay

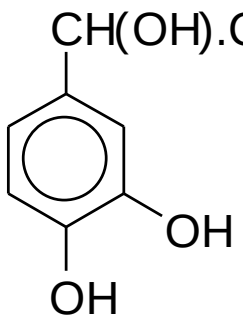
Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.3 g and *crystal violet solution* as indicator. Each ml of 0.1M *perchloric acid VS* is equivalent to 18.32 mg of C9H13NO3.

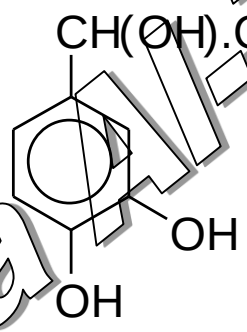
Q1: Write the titration equation ?

Q2: How we got the Nr. 18.32?

Q3: If the titration required to the end point 16.37 ml , (F=1)

what is the % purity of the substance ?

1. 

+ CH_3COOH ⟶ 

+ $CH_3COO^{\ominus}$

2. $HClO_4 + CH_3COOH \longrightarrow CH_3COOH_2^{\oplus} + ClO_4^{\ominus}$

3. $CH_3COO^{\ominus} + CH_3COOH_2^{\oplus} \longrightarrow 2CH_3COOH$

Metronidazole Suppositories

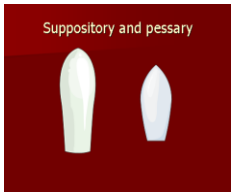
Content of metronidazole, $C_6H_9N_3O_3$

92.5 to 107.5% of the stated amount.

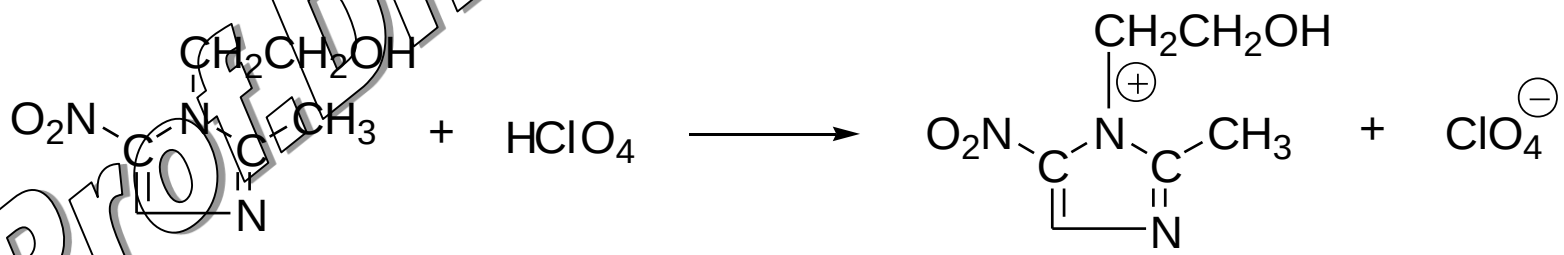
ASSAY تكون العينة هنا وزنية حيث يؤخذ الوزن المكافىء بعد صهر التحاميل

Weigh five suppositories, melt together by warming and allow to cool, stirring continuously until the mass is set. To a quantity containing 0.2 g of Metronidazole add 60 ml of *anhydrous acetic acid*, previously neutralised to *1-naphtholbenzein solution* with 0.1M *perchloric acid VS*, warm at 30° for 30 minutes and shake for 5 minutes. Cool and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *1-naphtholbenzein solution* as indicator. Each ml of 0.1M *perchloric acid VS* is equivalent to 17.12 mg of C6H9N3O3.

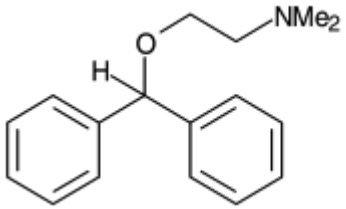
Metronidazole Suppositories



- Calculate the % content of metronidazole in the dosage form if you request to the end point 11,6 ml of Perchloric acid (F= 1.02).



Diphenhydramine Hydrochloride



291.8 $C_{17}H_{21}NO,HCl$

ASSAY

Dissolve 0.250 g in 20 ml of *anhydrous acetic acid R* , 5 ml of acetic acid anhydride and add 10 ml of *mercuric acetate solution R*. Titrate with *0.1*M *perchloric acid* and using 0.05 ml of *crystal violet solution R* as indicator.

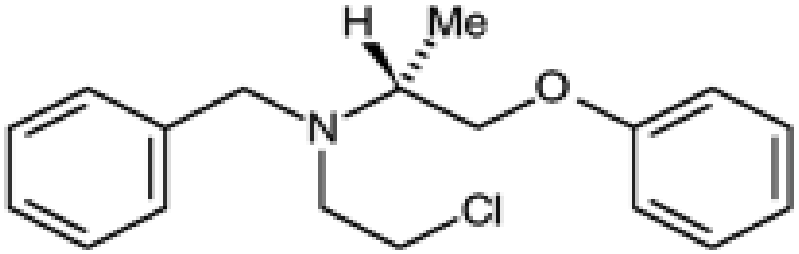
1 ml of *0.1*M *perchloric acid* is equivalent to 29.18 mg of $C_{17}H_{22}ClNO$.

1- Why we used acidic acid anhydride? And why we used mercuric acetate?

2- How we got the Nr. 29.18?

3- If we consumed to the end point 8.5 ml and F=0.99 , What is the purity %?

Phenoxybenzamine Hydrochloride



,HCl

حاجبات ألفا ، خافض ضغط الناتج

عن ورم لب الكظر

تفرغ 20 كبسولة بعد وزنها وبعد ازالة البقايا بالهواء أو محل عضوي تجفف ويعاد وزنها ويطرح من الوزن الكلي

$C_{18}H_{22}ClNO,HCl$ 340.3

Action and use

Alpha-adrenoceptor antagonist.

Preparation

Phenoxybenzamine Capsules

DEFINITION

Phenoxybenzamine Hydrochloride is (*RS*)-benzyl (2-chloroethyl)1-methyl-2-phenoxyethylamine hydrochloride. It contains not less than 98.5% and not more than 101.0% of $C_{18}H_{22}ClNO,HCl$, calculated with reference to the dried substance.

Phenoxybenzamine Capsules

Content of phenoxybenzamine hydrochloride, C18H22ClNO,HCl

92.5 to 107.5% of the stated amount

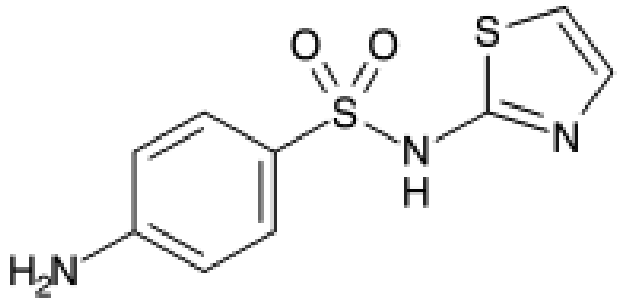
ASSAY

Weigh 20 capsules. Open the capsules carefully without loss of shell material, remove the contents, wash the shells with three 10 ml quantities of *chloroform* and add the washings to the capsule contents. Allow the shells to dry at room temperature to constant weight. The difference between the weights represents the weight of the total contents. Evaporate the mixed capsule contents and washings to dryness, stirring continuously, and carry out Method I for *non-aqueous titration*, Appendix VIII A, adding 10 ml of *mercury(II) acetate solution* and using *oracet blue B solution* as indicator. Each ml of 0.1M *perchloric acid VS* is equivalent to 34.03 mg of C18H22ClNO,HCl.

Titration of Drugs with acidic characters.

- Solvent ((DMF, Pyridine or an aprotic)
- Titrants : Na or lithium methoxide in methanol or tetrabutylammoniumhydroxide in dimethylformamide.
- End- point detection may be carried out with thymol blue as indicator or pot.metry
- Barbiturate , Sulphonamides and uracils

Sulfathiazole



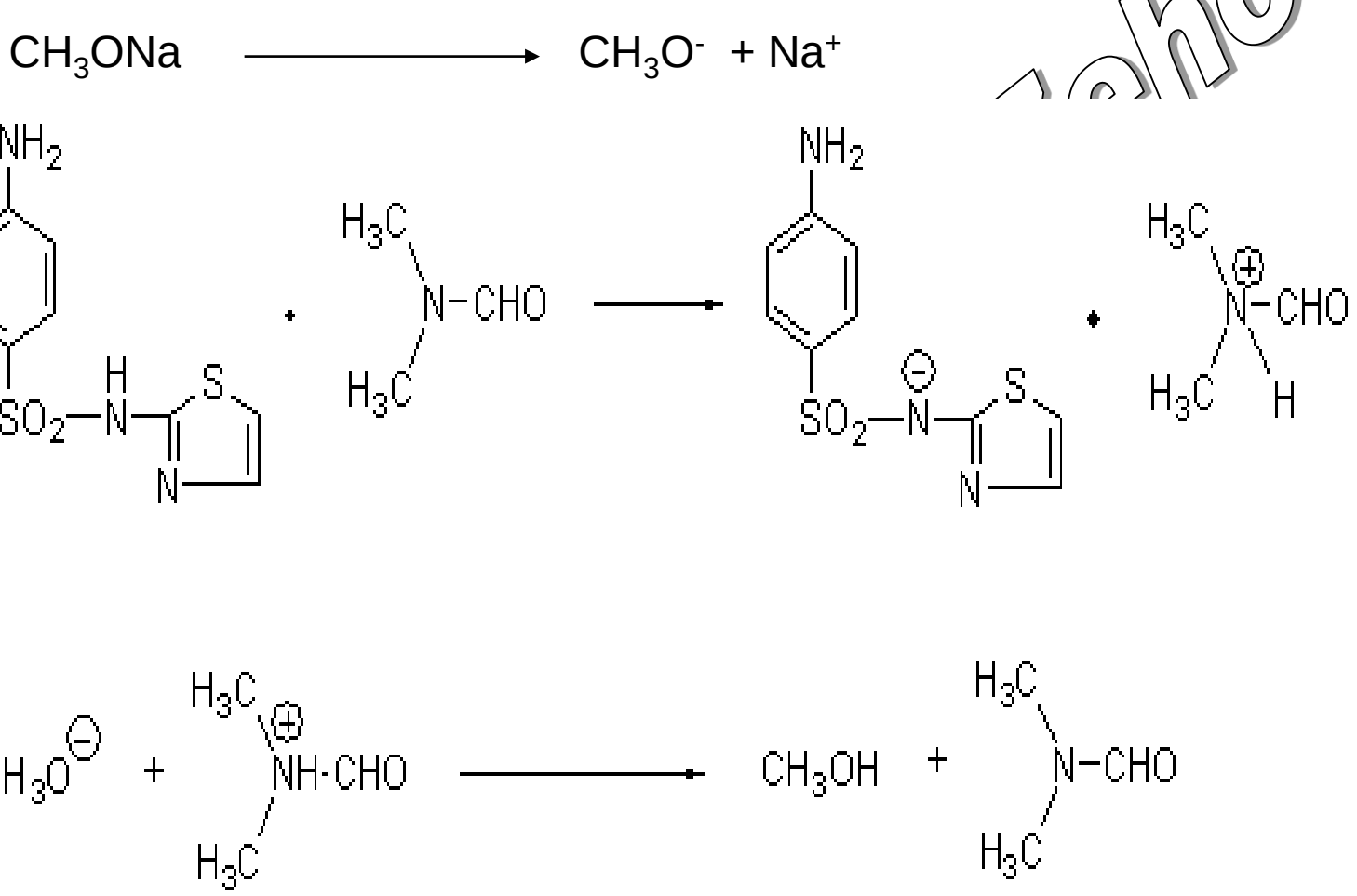
255.3 $C_9H_9N_3O_2S_2$

ASSAY

Dissolve 0.2 gram of sulphathiazole in 20 ml of DMF , add 2 drops of thymol blue solution which prepared in DMF .

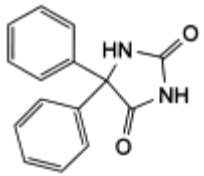
Titrate with 0.1 M Sodium methoxide solution VS, until the color change from yellow to blue.

Each 1 ml of 0.1 M of $NaOCH_3$ is equivalent to 0.025532 gram of $C_9H_9N_3O_2S_2$.



CH_3O^- + IND ⟶ Color change

Phenytoin



$C_{15}H_{12}N_2O_2$ 252.3

Action and use

Anticonvulsant.

Phenytoin Capsules

Content of phenytoin sodium, $C_{15}H_{11}N_2NaO_2$

92.5 to 107.5% of the stated amount.

ASSAY

Separation Methods
For many analytical methods, separating the analyte from potential interferents is a vital step in the procedure.

Shake a quantity of the mixed contents of 20 capsules containing 0.25 g of Phenytoin Sodium with 40 ml of 0.01M *sodium hydroxide* for 5 minutes and dilute to 50 ml with 0.01M *sodium hydroxide*. Centrifuge, acidify 25 ml of the clear liquid with 10 ml of 0.1M *hydrochloric acid* and extract with successive quantities of 50, 40 and 25 ml of *ether* . Wash the combined extracts with 10 ml of *water* , evaporate to dryness and dry the residue at 105°. Dissolve in 50 ml of *anhydrous pyridine* and carry out Method II for *non-aqueous titration*, Appendix VIII A, using 0.1M *tetrabutylammonium hydroxide VS* as titrant and a 0.3% w/v solution of *thymol blue* in *anhydrous pyridine* as indicator. Each ml of 0.1M *tetrabutylammonium hydroxide VS* is equivalent to 27.43 mg of C15H11N2NaO2.

Appendix VIII A. Non-aqueous Titration

(No Ph. Eur. method)

Method I

Dissolve the prescribed quantity of the substance being examined in a suitable volume of *anhydrous acetic acid* previously neutralised using the indicator specified in the monograph, warming and cooling if necessary, or prepare a solution as directed. When the substance is a salt of hydrochloric or hydrobromic acid, add 15 ml of *mercury (II)acetate solution* before neutralising the solvent, unless otherwise directed in the monograph. Titrate with 0.1M *perchloric acid VS* to the colour change of the indicator that corresponds to the maximum absolute value of dE/dV (where E is the electromotive force and V is the volume of titrant) in a *potentiometric titration,* Appendix VIII B, of the substance being examined. The indicator specified in the monograph is also used for the neutralisation of the *mercury (II)acetate solution* and the standardisation of the titrant.

When the temperature ($t2$) of the titrant at the time of the assay differs from the temperature ($t1$) of the titrant when it was standardised, multiply the volume of the titrant required by [1+0.0011($t1$ - $t2$)] and calculate the result of the assay from the corrected volume.

Carry out a blank titration when necessary.

Method II

The titrant, solvent and, where necessary, the indicator to be used are stated in the monograph.

Protect the solution and titrant from atmospheric carbon dioxide and moisture throughout the determination.

Dissolve the substance being examined in a suitable volume of the solvent previously neutralised to the indicator, warming and cooling if necessary, or prepare a solution as directed. Titrate to the colour change of the indicator that corresponds to the maximum absolute value of dE/dV (where E is the electromotive force and V is the volume of titrant) in a *potentiometric titration,* Appendix VIII B, of the substance under examination. The titrant is standardised using the same solvent and indicator as specified for the substance.

Carry out a blank titration when necessary.

Some dosage form which assayed in acid- base titration in non- aqueous media

Amodiaquine Tablets	0.1 M $HClO_4$	naphtholbenzein	0.01789
Bupivacaine Injection	0.1 M $HClO_4$	Crystal violet	0.03249
Chlormethiazole Capsules	0.1 M $HClO_4$	Crystal violet	0.01617
Choline Salicylate Ear drops.	0.1 M $HClO_4$	Methylorange	0.02413
Cytarabine Injection	0.1 M $HClO_4$	naphtholbenzein	0.02432
Demeclocycline Caps.	0.1 M $HClO_4$	Crystal violet	0.03395
Dextromoramide Injection	0.1 M $HClO_4$	naphtholbenzein	0.00785
Dextromoramide Tablets	0.1 M $HClO_4$	Crystal violet	0.00785
Demeclocyline	0.1 M $HClO_4$	Crystal violet	0.03395

Some dosage form which assayed in acid- base titration in non- aqueous media

Demeclocyline Capsules	0.1 M $HClO_4$	Crystal violet	0.03395
Dihydrocodeine Tablets	0.1 M $HClO_4$	Crystal violet	0.00903
Dothiepine Caps.	0.1 M $HClO_4$	Methyl orange	0.03319
Ethambutol Tablets	0.1 M $HClO_4$	naphtholbenzein	0.01386
Fluphenazine Decanoate Injection	0.1 M $HClO_4$	Crystal violet	0.02959
Fluphenazine Enthate inj.	0.1 M $HClO_4$	Crystal violet	0.02749
Inositol Nieotinat	0.1 M $HClO_4$	naphtholbenzein	0.01351

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Some dosage form which assayed in acid- base titration in non- aqueous media

Levodopa Caps.	0.1 M $HClO_4$	Oracet blue	0.01972
Levodopa Tab.	0.1 M $HClO_4$	Oracet blue	0.01972
Meclozine Tab.	0.1 M $HClO_4$	Oracet blue	0.02319
Metronidazole Supp.	0.1 M $HClO_4$	naphtholbenzein	0.01712
Nortriptyline Caps.	0.1 M $HClO_4$	naphtholbenzein	0.005268
Pethidine inj.	0.1 M $HClO_4$	Oracet blue	0.00567
Phenindomine Tab.	0.1 M $HClO_4$	Oracet blue	0.008229
Phenoxy benz-Amin Caps.	0.1 M $HClO_4$	naphtholbenzein	0.03403
Pethidine Tab.	0.1 M $HClO_4$	naphtholbenzein	0.01419
Prenylamine Tab.	0.1 M $HClO_4$	naphtholbenzein	0.03292
Propantheline Tab.	0.1 M $HClO_4$	Crystal violet	0.04489

Prof. J. Al-Zehouri

Q&A