Residual Titrations

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Definitions

"Titrant 1" is the chemical added to react with the analyte; usually the amount is in excess, and is a constant amount

"Titrant 2" is the chemical added to react with the excess "Titrant 1"; the amount added is variable

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Example: Codeine Assay

(Codeine: pK_a = 6.05, therefore pK_b = 7.95)

***USP 30*, Vol. 2, page 1824**

Assay -- Dissolve about 400 mg of Codeine, previously dried and accurately weighed, by warming it in 30.0 mL of 0.1 N sulfuric acid VS. Cool, and add 10 mL of water. Add methyl red TS, and titrate the excess acid with 0.1 N sodium hydroxide VS. Perform a blank determination (see *Residual Titrations* under *Titrimetry* <541>). Each mL of 0.1 N sulfuric acid is equivalent to 29.94 mg of $C_{18}H_{21}NO_3$.

"Titrant 1" = sulfuric acid, "Titrant 2" = sodium hydroxide

The Reasons

- Used to determine an analyte where the forward reaction is slow or thermodynamically unfavorable (Hydrolysis of esters)
- Used to determine an analyte when the analyte does not react directly with the titrant (Bromination reactions)
- Solubility problems
- Secondary reactions
- Endpoint determination not possible (Metal ion titrations)
- Several reasons may apply

Additional Equipment or Chemicals

- Refluxing often necessary to speed reaction or create the titratable species
- Waiting period is frequent
- Need a second “titrant” of known concentration

Forward vs. Residual Titration

- All requirements of a forward titration still apply in a residual titration
- Need the amount of “titrant 1” required to react with the analyte
- Difference between forward and residual titration = Amount of “titrant 1” is determined indirectly with residual titration

Basic Equation

Residual titrations use same four equations as forward titration:

1. Molarity Titrant X Liter Titrant = Moles Titrant (or mmol if mL are used)
2. Moles Titrant X Reaction ratio = Moles Titrate (or mmol if mL)
3. Moles Titrate X Formula Weight Titrate = Grams Titrate (or mg if mmol)
4. Grams Titrate X 100/(Grams Sample X Correction Factor) = % Titrate

These equations combine to produce the overall residual equation:

$$\% = \frac{\text{Molarity T2 X (Blank T2 - Assay T2) X RR X Formula Weight X 100}}{\text{Correction Factor X Weight Sample}}$$

where: RR = Reaction Ratio

Basic Equation, cont.

- Blank T2 is volume of titrant 2 needed to react with “titrant 1”
- Assay T2 is volume of titrant 2 needed to react with excess titrant 1 after titrant 1’s reaction with the analyte
- “Blank - Assay” would then be volume of titrant 2 needed to react with the analyte only
- Reaction ratio equals moles titrate/moles titrant 2 in the balanced equation(s)
- Concentration of titrant 1 does not appear in above calculation (USP procedures often specify titrant 1 in the titer; based on an alternate calculation that can be derived)

Blank Titration

- Can be used to determine the concentration of titrant 2
- Conversely, if concentrations of titrant 1 and titrant 2 are known, and titrant 1 is not used by any other means in the solution, then blank titration is not needed

Alternate Equation for USP Titer

To get the titer, best to compute in steps

- (The derivation of the equation is complex and will be presented in the advanced residual titration module)

Indications of “success”

For a “well-behaved” residual titration:

- The blank volume is greater than or equal to the Assay volume (at least several milliliters greater)
- Replicate determinations of the blank should have a low RSD (several tenths of a percent or less)

Sources of Errors

- Same as with forward titrations
  - (e.g., avoid losing sample, carbon dioxide)
- When scaling down a procedure, avoid making titrant 1 a limiting reagent

Why avoid Titrant 1 as a Limiting Reagent?

Glycerin Assay, USP 30, Vol. 2, page 2240, and

Glycerin Suppositories Assay USP 30, Vol 2, page 2241

Both use periodate to form titratable species.

REACTIONS:

$CH_2(OH)\text{-}CH(OH)\text{-}CH_2(OH) + 2IO_4^- \rightarrow HCOOH + 2H_2CO + H_2O + 2IO_3^-$

$IO_4^- + 7I^- + 8H^+ \rightarrow 4I_2 + 4H_2O$ and $IO_3^- + 5I^- + 6H^+ \rightarrow 3I_2 + 3H_2O$

- The **Glycerin Assay** is a direct titration of the formic acid formed. The **Glycerin Suppositories Assay** is a residual titration determining how much oxidizing power (iodate and periodate) remains after reaction.
- Only 25% of the periodate oxidizing power is consumed by the glycerin. Any amount of glycerin that exceeds 25% of the periodate power will not be reacted.
- The result of this will be low assay values.

Example: Lithium Carbonate Assay

(Addition of acid to carbonate gives off carbon dioxide. This affects pH and causes problems with pH or colorimetric measurement.)

USP 30, Vol. 2, page 2484

Assay -- Dissolve about 1 g of Lithium Carbonate, accurately weighed, in 50.0 mL of 1 N sulfuric acid VS, add methyl orange TS, and titrate the excess acid with 1 N sodium hydroxide VS. Perform a blank determination (see Residual Titrations under Titrimetry <541>). Each mL of 1 N sulfuric acid is equivalent to 36.95 mg of Li_2CO_3.

Lithium Carbonate, cont.

Data

Weight Lithium Carbonate: 1.0025 g

LOD: 0.25%

Molarity sodium hydroxide VS: 1.040 M (N)

Volume of sodium hydroxide in Assay: 23.50 mL

Volume of sodium hydroxide in Blank: 49.50 mL

T1 = sulfuric acid, T2 = sodium hydroxide

Lithium Carbonate, cont.

Equations

- $Li_2CO_3 + H_2SO_4 \rightarrow Li_2SO_4 + H_2O + CO_2$
- $H_2SO_4 + 2NaOH \rightarrow Na_2SO_4 + 2\ H_2O$

Using overall equation

$$\% = \frac{\text{Molarity T2 X (Blank T2 - Assay T2) X RR X Formula Weight X 100}}{\text{Correction Factor X Weight Sample}}$$

$$\% = \frac{1.040\ M\ \text{X}\ (49.50 - 23.50)\ \text{mL X 0.5 X 73.89 mg/mmol X 100}}{(1 - 0.0025)\ \text{X 1002.5mg}}$$

where: RR = reaction ratio

- % = 99.9%

Steps

- mL of NaOH equivalent to Li_2CO_3 = 49.50 mL - 23.50 mL = 26.00 mL
- mmol of NaOH equivalent to Li_2CO_3 = 26.00 mL X 1.040 *M* = 27.04 mmol
- mmol of Li_2CO_3 = 27.04 mmol X $1Li_2CO_3$ /2NaOH = 13.52 mmol
- mg of Li_2CO_3 = 13.52 mmol X 73.89 mg/mmol = 998.99 mg
- corrected weight of sample = (1 - 0.0025) X 1002.5 mg = 999.99 mg
- % Assay = 998.99 mg X 100/ 999.99 mg = 99.9%

Note: Same numerical values were used as were used in the overall equation

Conclusion

Residual Titrations look difficult, but they are not.

If you:

- know the chemistry (including balanced reactions)
- know what to expect, and
- know the pitfalls and the sources of error

you should succeed.