REVIEW

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Problems in the interpretation of nonaqueous titrations

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Most phenomena (like promoting and leveling as well as differentiating effects) of common nonaqueous titrations can be explained by the Brönsted's concept combined with the hydrogen bond theory but some open problems are shown in connection with the use of formic acid and/or acetic anhydride.

1. Introduction

Since the nonaqueous titrations are quantitative, exact and well reproducible, they are preferred in pharmaceutical analysis: there are over 100 assays based on this method in the European Pharmacopoeia and a similar order of magnitude can be estimated in the United States Pharmacopoea 24 (in spite of the fact that HPLC and similar methods are sometimes preferred). The use of different solvents and additives has increased because as a general policy one tries to avoid the application of toxic reagents (and solvents) (Miller 1996). For example, for the quantitative analysis of halide salts of organic bases, solutions in glacial acetic acid/acetic anhydride or formic acid/acetic anhydride are proposed instead of the mercuric acetate method (Miller 1996). The methods work well in practice, but their interpretation is rather inconsistent: the theories and suppositions of the 1920's and 1930's are applied and sometimes confused. In the present paper the usual interpretations of such titrations are surveyed with an emphasis on some problematic points. Some new aspects based on experimental facts will be discussed in a following paper.

2. A general background

The nonaqueous acid-base titrations are currently used to a great extent in analytical chemistry (Kolthoff and Bruckenstein 1959; West 1960; Charlot and Trémillon 1969; Gyenes 1970; Streuli 1975; Šafařik and Stránský 1986). As the first step, the compound to be titrated is dissolved in an appropriate solvent (which is generally a protogenic one for bases and a protophilic one for acids). The Table presents some important solvents and their relative permittivities according to the classification of Brönsted (Brönsted 1928).

Indicating the component of acidic character as HA and using the symbol B for bases, the interactions can be characterized (Pimentel and McClellan, 1960) by the following equilibria:

$$B + HA \Leftrightarrow B \cdots HA \Leftrightarrow BH^{+} \cdots A^{-} \Leftrightarrow BH^{+} + A^{-} \quad (1)$$

where $\cdots$ stands for hydrogen bonding. It follows that $B \cdots HA$ indicates an H-bonded complex, while $BH^{+} \cdots A^{-}$ is an H-bonded ion pair.

The equilibrium at the right is shifted towards the dissociation of the H-bonded ion pair only in solvents of high relative permittivity (dielectric constant, ε_r), like water. Since the usual solvents in nonaqueous titrations have much lower ε_r than that of water (see Table), the H-bonded ion pair can be regarded as the end product of the acid-base interactions (Barcza and Buvári-Barcza 2003).

Applying eq. (1) for the interaction of a N-base and glacial acetic acid (AcOH, the solvent mostly used in the determination of bases):

$$\begin{aligned} &AcOH + N\equiv \; \Leftrightarrow AcOH \cdots N\equiv \\ &\Leftrightarrow AcO^{-} \cdots {}^{+}H{-}N\equiv \; (\Leftrightarrow AcO^{-} + \equiv N{-}H^{+}) \qquad (2) \end{aligned}$$

As titrant, perchloric acid in glacial acetic acid is commonly used. In this solution, AcOH is forced to undertake the unusual role of a base:

$$\begin{aligned} &AcOH + HClO_4 \Leftrightarrow AcOH \cdots HClO_4 \\ &\Leftrightarrow AcOH_2^{+} \cdots ClO_4^{-} (\Leftrightarrow AcOH_2^{+} + ClO_4^{-}) \qquad (3) \end{aligned}$$

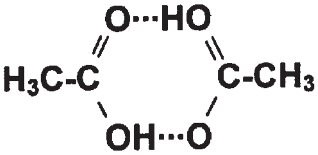
Table: Classification of solvents widely used in analytical chemistry

Class	Property	Solvent (ε_r)
Protogenic ("acidic")	Proton donor HA	Acetic acid (6,13) Propionic acid (3,44) Formic acid (58,5)
Protophilic ("basic")	Proton acceptor B	Pyridine (12,4) Ethylenediamine (14,2) n-Butylamin (4,88)
Amphiprotic ("water analogue")	Proton donor and proton acceptor HA + B	Water (78,54) Ethanol (24,53) Ethylene glycol (37,7)
Aprotic ("neutral")	N ((HA)) ((B))	n-Hexane (1,9) Chloroform (4,81) Methylisobutyl keton (12,92)

The general equation of the acid-base titration (in glacial acetic acid) is:

$$\begin{aligned}&\equiv\mathrm{N{-}H^+\cdots OAc^-} + \mathrm{AcOH_2^+\cdots ClO_4^-}\\&= \equiv\mathrm{N{-}H^+\cdots ClO_4^-} + \mathrm{(AcOH)_2}\end{aligned} \qquad (4)$$

where $(AcOH)_2$ symbolizes the unit of the solvent, the acetic acid dimer.



It can be seen that the protogenic solvents promote the basicity of the dissolved bases and at the same time level the differences among the bases. (Similarly, the protophilic solvents have promoting and leveling effects on the dissolved acids.) (Barcza and Buvári-Barcza 2003)

Considering the differentiating effect of glacial acetic acid (Barcza and Buvári-Barcza 2003), e.g. the organic acids are not acids at all since their carboxylic groups form reinforced H-bonded cyclic structures with acetic acid molecules (likewise the dimeric acetic acid, see the formula, but the hydrogen halides act as acids in glacial acetic acid, too, in spite of the fact that their acidities are much lower than that of perchloric acid. It follows that the organic acid salts of bases can be titrated in glacial acetic acid as pure bases but the hydrohalide salts cannot be measured directly.

Based on the fact that neither mercuric acetate nor mercuric chloride dissociate in glacial acetic acid, the halide (of a hydrohalide salt) can be exchanged easily for acetate, e.g.:

$$\begin{aligned}&2\equiv\mathrm{N{-}H^+\cdots Cl^-} + [\mathrm{Hg(AcO)_2}]\\&= 2\equiv\mathrm{N{-}H^+\cdots OAc^-} + [\mathrm{HgCl_2}]\end{aligned} \qquad (5)$$

and the acetate formed can be titrated directly (see eq. (4)). (The excess bisacetato mercuric(II) complex is not reactive towards perchloric acid, i.e. the excess of $Hg(AcO)_2$ does not disturb the determination.) The method creates an environmental hazard due to mercury pollution, however.

Formally, anhydrous formic acid as an acidic solvent fits well into this picture, in spite of the fact that its properties differ significantly from those of the next members of the homologous series (acetic and propionic acids). On the other hand, acetic anhydride [Ac_2O: $CH_3C(O)OC(O)CH_3$], which is an aprotic solvent but often used in the nonaqueous titration of bases also needs more careful deliberations.

2.1. *Formic acid as an acidic solvent of particular properties*

Although formic acid (HCOOH) belongs to the protogenic solvents, it differs from glacial acetic acid (and propionic acid, recommended sometimes) by the much higher dielectric constant (Table) and acidic strength. The ε_r value of acetic (and propionic) acid approaches zero, which is the consequence of the cyclic structure of the dimeric units, while formic acid is built up of linear oligomers, mostly linear dimers (see eq. (8)). The effect of this structure appears in the ionic product of the assumed autoprotolysis (Hammett and Deyrup 1932), calculated from conductivity data:

$$K_{ip} = [\mathrm{HC(OH)_2^+}][\mathrm{HCOO^-}] = 10^{-6.2} \qquad (6)$$

which differs again from the K_{ip} value of acetic acid ($= 10^{-14.45}$) (Bruckenstein and Kolthoff 1956).

The symbol $HC(OH)_2{}^+$ in eq. (6) does not correspond to any real chemical species but is meant to show that the proton is somehow solvated: protonated formic acid would likely decompose with the formation of carbon monoxide, and the proton is stabilized finally in the form of H_3O^+ (Zielinski et al. 1998). Therefore "perchloric acid in anhydrous formic acid" as a titrant cannot be produced and perchloric acid in glacial acetic acid must also be used as a titrant for the acid-base titrations in formic acid solutions.

The differences among the three mentioned acids can also be demonstrated in aqueous solutions, where the acidic dissociation constants of both monomeric and dimeric acids are:

$$K_{11} = \frac{[\mathrm{H^+}][\mathrm{A^-}]}{[\mathrm{HA}]} \quad \text{and} \quad K_{12} = \frac{[\mathrm{H^+}][\mathrm{HA_2^-}]}{[\mathrm{H_2A_2}]} \qquad (7)$$

The measured values (in 1.00 M $NaClO_4$ at 25 °C) are as follows: formic acid, $K_{11} = 3.19 \times 10^{-4}$ and $K_{12} = 3.2 \times 10^{-3}$; acetic acid, $K_{11} = 2.84 \times 10^{-5}$ and $K_{12} = 5.2 \times 10^{-5}$; propionic acid, $K_{11} = 2.88 \times 10^{-5}$ and $K_{12} = 1.5 \times 10^{-5}$ (Barcza and Mihályi 1977). As can be seen, the monomeric and dimeric acetic (as well as propionic) acids have practically identical acidic constants. The constant for the monomeric formic acid is ten times higher, and the dimeric formic acid:

$$\begin{aligned}&\mathrm{O{=}CH{-}OH\cdots O{=}CH{-}OH}\\&\Leftrightarrow \mathrm{O{=}CH{-}OH\cdots O{=}CH{-}O^-} + \mathrm{H^+}\end{aligned} \qquad (8)$$

is again ten times stonger acid than its monomeric form. This fundamental difference can be explained by the electron withdrawing effect of the accumulated oxygens in the hydrogen-bis(formate) ion.

Extrapolating this picture for solutions of bases in anhydrous formic acid, a small dissociation constant and the H-bonded ion pair formation between protonated base and hydrogen-bis(formate) ion (instead of AcO^-) are formal differences in eq. (2). The essential difference is that the linear associates (mostly dimers) of formic acid are much stronger acids than the (cyclic) dimeric acetic acid is, therefore they are able to protonate very weak bases (like caffeine, theobromine, etc.) so allowing their titration (Reiss 1959).

2.2. *Is acetic anhydride an "acidic" solvent?*

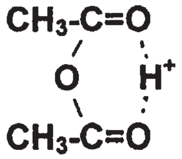
Since acetic anhydride (Ac_2O) is also used alone or in mixtures during the nonaqueous determinations of bases with good results, sometimes it is grouped among the acidic solvents even in some textbooks. Considering the formula, it is clear that it cannot be a protogenic solvent; on the contrary molecules of acetic anhydride are able to bind protons by the lone pair electrons of the oxygens, i.e. they are strictly proton acceptors (Mackenzie and Winter 1948):

$$\mathrm{Ac_2O} + \mathrm{H^+} \Leftrightarrow \mathrm{Ac_2OH^+} \Leftrightarrow \mathrm{AcOH} + \mathrm{Ac^+} \qquad (9)$$

where AcOH means acetic acid, while Ac^+ is acetyl cation (CH_3CO^+). Based on kinetic measurements (Wimer 1958), the following order of relative acidity can be assumed for the species existing in the system:

$$\mathrm{AcOH_2^+} < \mathrm{Ac_2OH^+} < \mathrm{Ac^+} \qquad (10)$$

Protonation of the acetic anhydride (formation of Ac_2OH^+) is possible not only by protonation of the oxygen connecting the two carbonyl groups, but also by protonation of the two carbonyl oxygens, forming an intramolecular H-bond. Because the rotation barriers in Ac_2O molecules are very low (Wu et al. 2000), the existence of this species is highly probable.



Disregarding the possible protonation reactions, acetic anhydride is usually mentioned as an inert solvent but with an assumed tendency to dissociate. This dissociation can also be characterized with a K_{ip} constant (Jander and Surawski 1961):

$$Ac_2O \Leftrightarrow Ac^+ + AcO^-$$
$$K_{ip} = [Ac^+][AcO^-] = 10^{-14.5} \qquad (11)$$

The fundamental problem is that the equilibrium concentration of acetyl cation is very low because of the relatively low ε_r value (22.1) and the extremely weak solvation ability of Ac_2O. The existence of Ac^+ can be proven first by kinetic analyses and its further existence depends on the other species present in the solution.

2.3. The acetylation reactions of acetic anhydride

It is known that tertiary amines can be separately titrated with perchloric acid in a mixture of amines (Kolthoff and Bruckenstein 1959; West 1960; Gyenes 1970; Streuli 1975) when the primary and secondary amines are previously acetylated (in a relatively slow reaction) by acetic anhydride, e.g.:

$$R_2NH + Ac_2O \rightarrow R_2NAc + AcOH \qquad (12)$$

(The presence of amides formed does not influence the titration.)

Alcohols can be similarly acetylated:

$$ROH + Ac_2O = ROAc + AcOH \qquad (13)$$

(under formation of esters).

From the point of view of analytical chemistry, the reaction with water is of first importance, e.g. in preparing a perchloric acid titrant in glacial acetic acid:

$$H_2O + Ac_2O = 2\,AcOH \qquad (14)$$

Formic acid as a solvent always contains some water (since it is unstable in absence of water) but water should disturb the nonaqueous titrations, it is generally used in mixtures with acetic anhydride. But the interaction of the components can slowly lead to the formation of a mixed anhydride:

$$HC(O)OH + Ac_2O \rightarrow HC(O)OAc + AcOH \qquad (15)$$

HC(O)OAc is not a stable compound, it is decomposed slowly under the formation of CO and AcOH (Zielinski et al. 1998).

The generalized form of eq. (15) is valid for every organic acids:

$$R{-}COOH + Ac_2O \rightarrow R{-}C(O)OAc + AcOH \qquad (16)$$

producing mixed anhydrides.

Inorganic oxoacids form also mixed anhydrides in acetic anhydride, e.g. sulfuric acid (Russel and Cameron 1938):

$$H_2SO_4 + Ac_2O \Leftrightarrow AcOH + AcOS(O_2)OH \qquad (17)$$

where the monobasic acetyl sulfuric acid [$AcOS(O_2)OH = CH_3C(O)OS(O_2)OH$] is a very strong acid (a “superacid”), but it is unstable and slowly converted into the (divalent) sulfoacetic acid:

$$CH_3C(O)OS(O_2)OH \rightarrow HOS(O_2)CH_2COOH \qquad (18)$$

Phosphoric acid is supposed to react similarly (Streuli 1958) under the formation of a monobasic strong acid [diacetyl phosphoric acid: $(AcO)_2P(O)OH$].

The reaction of hydrogen halides with acetic anhydride is fundamentally identical:

$$HX + Ac_2O \Leftrightarrow AcX + AcOH \qquad (19)$$

and the acetyl halides behave in Ac_2O solution practically as inert molecules (because of the stable $C - X$ bonds) in acid-base interactions.

From the point of view of acid-base titrations, the interaction with halide ions is more interesting, e.g.:

$$F^- + Ac_2O = AcF + AcO^- \qquad (20)$$

By using this reaction as a first step, fluorides can be converted to acetate in Ac_2O and titrated with perchloric acid in glacial acetic acid (West 1960; Gyenes 1970; Streuli 1975; Šafařik and Stránský, 1986).

In contrast to the fluorides, the reactions of the chlorides and bromides are not always quantitative; e.g., the hydrochlorides of lidocaine or quinine (moreover the cetylpyridinium chloride) can be measured quantitatively as bases this way, while hydrochloride salts of some other bases cannot (Miller 1996).

It is rather unexpected that perchloric acid, which is widely used in analytical chemistry, is discussed along with the hydrogen halides in spite of the fact that it is a typical oxoacid. Acetyl perchlorate can be prepared not only in the reaction of perchloric acid and Ac_2O, but also from $AgClO_4$ and AcBr (Jander and Surawski 1961). $AcClO_4$ reacts in Ac_2O as a strong acid (cf. eq. (10)), but the solution is unstable and decomposes slowly as shown by its deepening yellow colouration. This colour suggests that $AcClO_4$ must be also regarded as a mixed anhydride, where the tetrahedral symmetry of perchlorate is distorted.

Acetyl perchlorate can be better modelled by the well known halogen perchlorates ($XOClO_3$) (Greenwood and Earnshaw 1990) than by acetyl halides. Because of the decomposition, perchloric acid solutions must also be made with glacial acetic acid for the acid-base titrations in Ac_2O (Russel and Cameron 1938).

3. Summary

In the treatment of acid-base reactions, the Brönsted’s concept combined with the hydrogen bond theory has proven most useful in analytical chemistry. Not only the promoting and leveling effects can be easily explained but also the differentiating effect.

In spite of the fact that some properties of formic acid differ highly from those of other monocarboxylic acids, it is unambiguously a protogenic solvent.

Acetic anhydride is obviously not an acidic but an aprotic (very slightly protophilic) solvent. Its effect in acid-base titration is unexplained but the acetylation reactions appears to be very important.

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