

CHEMICAL METHODS OF ANALYSIS

THE PRINCIPLES OF THE USE OF NONAQUEOUS SOLVENTS FOR ACID-BASE TITRATIONS

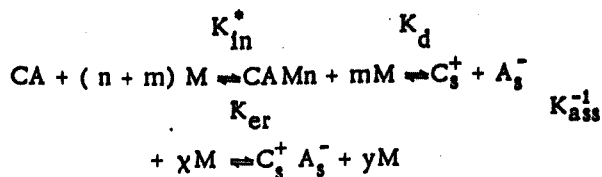
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Depending on the solvent, a given substance may be a nonelectrolyte or a strong or weak electrolyte, and it may be an acid, base, or salt. The acidity, basicity, strength, solubility, and other properties of electrolytes change under the influence of nonaqueous solvents. This means that the range of acid-base titrations can be greatly extended, to include very weak acids and bases and mixtures of acids and bases of similar strengths. Up till now the majority of investigators have used empirical means for developing titration methods, and have not based their choice of solvents and titration conditions on theoretical considerations as to the effects of solvent on strength of acid and base. It is therefore pertinent to consider the theoretical basis of the use of nonaqueous solvents for titration.

The Theoretical Basis of Titration in Nonaqueous Solvents

The dissociation of an electrolyte is a complex process [1, 2] proceeding in several successive stages. It may be represented as follows:



where $K_{in}^* = \frac{a_{CA}^*}{a_{CAMn}^*}$ is the instability constant,

$K_d = \frac{a_{C_s}^* + a_{A_s^-}^*}{a_{CAMn}^*}$ is the dissociation constant,

$K_{ass}^{-1} = \frac{a_{C_s}^* + a_{A_s^-}^*}{a_{C_s}^* + a_{A_s^-}^*}$ is the association constant,

$K_{tr} = \frac{a_{C_s}^* + a_{A_s^-}^*}{a_{CAMn}^*} = K_d K_{ass}$ is the transformation constant, and $m = x + y$.

The dissociation constant measured in the normal way (K_n) expresses the ratio of the product of the activities of the free ions to the total activity of the undissociated part of the electrolyte:

$$K_n = \frac{a_{C_s}^* + a_{A_s^-}^*}{a_{undiss}^*}$$

This normal constant can be expressed in terms of the equilibrium constants:

$$K_n = \frac{K_d}{1 + K_{in}^* + K_{tr}} \quad (1)$$

This expression can have very different values, depending on the electrolyte and the solvent.

The theory of dissociation of electrolytes in different solvents is based on these ideas, and on the quantitative calculation of the mutual affinity of the ions of the dissociating substance in vacuo and of the energy of solvation of the ions and of the solvent molecules. The quantitative relation between the strength of an electrolyte and the properties of the material and of the solvent can be expressed by the equation

$$K_n = K \exp \frac{\sum A_x - A_{mol}}{RT} \quad (2)$$

Here K , the dissociation constant of the electrolyte in vacuo, is determined by the mutual affinity of the ions of the dissociating substance in vacuo. The value of K for an acid is determined by the affinity between the acid anion and a proton. This affinity is characterized by the particular acidity constant of the acid in vacuo

$$K_a = \frac{a_{H^+} a_{A^-}}{a_{HA}} \quad (3)$$

and, for a base, by the particular basicity constant

$$K_b = \frac{a_{BH^+}}{a_{H^+} a_B} \quad (4)$$

which is the reciprocal of the particular acidity constant of the BH^+ ion.

The value of A_{mol} , the solvation energy of a molecule, depends on the composition and complexity of the addition products formed, and is determined by the energy of condensation of the molecule CA and the energy of its solvation:

$$A_{mol} = A_{con} + A_{s,s} \quad (5)$$

In the simplest case the energy $A_{s,s}$ depends on the stability of the addition product and on the extent of transformation of the molecule into these products and ion pairs.

The value of $\sum A_x$ represents the total chemical energy of solvation of the ions:

$$\sum A_x = A_{xC^+} + A_{xA^-} \quad (6)$$

For any acid, A_{xC^+} is the energy of solvation of a proton. This energy is the sum of the energy of combination of a proton with a solvent molecule in vacuo to form lyonium ion MH^+ and the energy of further solvation of this ion, A_{MH^+} . For a base, the value of A_{xBH^+} express the energy of solvation of the ion BH^+ , formed from the base B , and A_{xA^-} is the energy of formation and further solvation of the solvate ion $(M-H)^-$.

The energies of formation of these solvent ions are determined by the affinities of the solvent molecule and anion for a proton in vacuo. In the theory of acids and bases these affinities are expressed in terms of the particular acidity constants of these ions

$$K_{a\ MH^+} = \frac{a_{H^+} a_M}{a_{MH^+}} \quad (7)$$

$$K_{a\ M} = \frac{a_{H^+} a_{(M-H)^-}}{a_M} \quad (8)$$

or in terms of the reciprocals of the basicity constants:

$$K_{a\text{MH}^+} = \frac{1}{K_{b\text{M}}} \quad (7a)$$

$$K_{a\text{M}} = \frac{1}{K_{b(\text{M-H})^-}} \quad (8a)$$

The energy of solvation of a proton can be given in terms of the particular acidity constant as

$$A_{x\text{H}^+} = -RT \ln K_{a\text{MH}^+} + RT \ln a_{\text{M}} + A_{x\text{MH}^+} \quad (9)$$

Similar, the solvation energy of an anion on dissociation of a base is given by

$$A_{x\text{A}^-} = -RT \ln K_{b(\text{M-H})^-} + RT \ln a_{\text{M}} + A_{x(\text{M-H})^-} \quad (10)$$

According to the theory developed by Bernal and Fowler [3] and by K. P. Mishchenko and A. S. Sukhotin [4], the solvation energy of an already formed ion is given, to a first approximation, by the equation

$$A_x = \frac{z^2 e^2}{2r} (1 - 1/D) + A_{\text{sol}} \quad (11)$$

The term A_{sol} represents the energy of all forms of interaction of the ion with the dipole molecules of solvent:

$$A_{\text{sol}} \approx n \frac{e \mu N}{D r^2}$$

Substituting the values of $A_{x\text{H}^+}$ for a proton and of $A_{x\text{A}^-}$ for a solvate anion in equation (2), we obtain the following special cases of this equation:

for salts

$$K_{\text{n}} = K \exp \frac{A_{x\text{K}^+} + A_{x\text{A}^-} - A_{\text{mol}}}{RT} \quad (12)$$

for acids

$$K_{\text{nA}} = \frac{K_{a\text{M}}}{K_{a\text{MH}^+}} \times \exp \frac{A_{x\text{MH}^+} + A_{x\text{A}^-} - A_{\text{mol}}}{RT} \quad (13)$$

for bases

$$K_{\text{nB}} = \frac{K_{b\text{M}}}{K_{b(\text{M-H})^-}} \times \exp \frac{A_{x\text{BH}^+} + A_{x(\text{M-H})^-} - A_{\text{mol}}}{RT} \quad (14)$$

for the ionic product of the solvent

$$K_{\text{l}}^* = \frac{K_{a\text{M}} \cdot a_{\text{M}}^2}{K_{a\text{MH}^+}} \times \exp \left[\frac{A_{x\text{MH}^+} + A_{x(\text{M-H})^-}}{RT} \right] \quad (15)$$

It follows from (13) that the strength of any acid will increase as the particular acidity constant of the onium ion decreases, i.e., with increasing basicity of solvent, and as the solvation energies $A_{x\text{MH}^+}$ and $A_{x\text{A}^-}$

increase, which occurs with increasing dielectric permeability of the solvent and dipole moment of its molecules. The values of $A_{x\text{A}^-}$ and A_{mol} are very similar for acids of a given type, e.g., carboxylic acids. The strengths of these acids therefore usually alter in a similar way with change of solvent. For any other type of acid, such as phenols, the changes in strength within the group are similar, but can differ considerably from the changes in acids of the first type. Thus, not only does the strength of an acid change with solvent, but so does the ratio of its strength to that of an acid of another type. Such differential effects on acid strengths are particularly characteristic of solvents of low dielectric permeability which do not contain hydroxyl groups (ketones, nitriles, acetic acid, etc.).

It follows in the same way from (14) that the strength of any base increases with decreasing basicity or increasing acidity of the solvent, and with increasing energy of solvation of the ions. The differential effects of solvents on the strengths of bases are determined by differences in the solvation energies of molecules and cations of base. In general, the differential effect with respect to bases is higher in solvents of low dielectric permeability and weak acidity, which do not contain a hydroxyl group [2].

Under otherwise similar conditions, the precision of the titration of an acid is determined by the ratio of the ionic product of the medium, K_{I}^* , to the dissociation constant of the acid, K_{nA} , i.e., the ratio $K_{\text{I}}^*/K_{\text{nA}}$. The precision of titration of a base is determined by the ratio $K_{\text{I}}^*/K_{\text{nB}}$ of a mixture of acids by $K_{\text{nAII}}/K_{\text{nAI}}$, and of a mixture of bases by $K_{\text{nBII}}/K_{\text{nBI}}$ [5]. These ratios, which determine the possibility of carrying out the titration, may in all cases be denoted by the symbol K_{t} , i.e., the titration constant. The smaller K_{t} the less is the titration error. Sufficient accuracy can be obtained in the titration of 0.1 N acids or bases, or mixtures of acids or bases, in equivalent proportions, under normal conditions, provided that K_{t} is of the order 10^{-4} or less. However, K_{t} should be less for the titration of more dilute solutions or when the components of a mixture are not in equivalent proportions.

K_{t} is fixed when acid-base titrations are carried out as usual in aqueous solution, and the precision can only be increased by using higher concentrations of the substance to be titrated, or by improving the sensitivity of the end-point determination (as by electrometric titration). But a change in concentration or concentration ratio does not have a very pronounced effect, and often cannot be used in analysis. Moreover, potentiometric determination of the end point only increases the precision by a factor of 2-3.

A much greater increase in the precision of a titration can be achieved by the use of nonaqueous solvents, where there can be considerable changes in the ratios of ionic product to dissociation constant of acid or base and their relationships to strength of acid or base. Indeed, the selection of a nonaqueous solvent can so reduce the value of K_{t} that it is possible to carry out a titration which would have been impossible in an aqueous solution.

The effects of solvents are so diverse that the values of K_{t} in nonaqueous solvents should always be determined experimentally. Adequate experimental data is now available for the properties of acids and bases in solution in alcohols, certain ketones, dioxane and its mixtures with water, acetic acid, formic acid, ammonia, formamide, pyridine, aniline, and some other solvents [1, 6, 7].

The choice of solvent may be made on the basis of the relation between K_{t} and solvent properties. Corresponding expressions for K_{t} can be derived from (12)-(15), and are given below.

For titration of acids:

$$K_{\text{t}} = \frac{K_{\text{I}}^*}{K_{\text{nA}}} = \frac{K_{\text{aM}} \cdot a_{\text{M}}}{K_{\text{a}}} \times \exp \left[\frac{A_{\text{x(M-H)}} - A_{\text{x A}^-} + A_{\text{mol}}}{RT} \right] \quad (16)$$

For titration of bases:

$$K_{\text{t}} = \frac{K_{\text{I}}^*}{K_{\text{nB}}} = \frac{K_{\text{bM}} \cdot a_{\text{M}}}{K_{\text{b}}} \times \exp \left[\frac{A_{\text{x MH}^+} - A_{\text{x BH}^+} + A_{\text{mol}}}{RT} \right] \quad (17)$$

For titration of mixtures of two acids:

$$K_{\text{t}} = \frac{K_{\text{nA II}}}{K_{\text{nA I}}} = \frac{K_{\text{a}_2}}{K_{\text{a}_1}} \exp \left[\frac{(A_{\text{x A II}^-} - A_{\text{x A I}^-}) - (A_{\text{mol A II}} - A_{\text{mol A I}})}{RT} \right] \quad (18)$$

For titration of mixtures of two bases:

$$K_T = \frac{K_{NB \text{ II}}}{K_{NB \text{ I}}} = \frac{K_{b_2}}{K_{b_1}} \exp \left[\frac{(A_{x \text{ BII H}^+} - A_{x \text{ BI H}^+}) - (A_{\text{mol BII}} - A_{\text{mol BI}})}{RT} \right] \quad (19)$$

The Choice of Titration Methods in Nonaqueous Media

All the possible uses of nonaqueous solvents can be classified, on the basis of the above equations, as shown in Table. 1.

Each case will be considered separately.

Case I. The Improvement of Conditions for Titrating Acids. This depends on decreasing the ratio K_1^*/K_{NA} . It can be evaluated quantitatively if there is experimental data available for the ionic product of the medium and for the dissociation constant of the acid. A general picture of the choice of solvent can be obtained from (14). This shows that improved titration conditions are achieved with solvents of low particular acidity constant, K_{AM} , i.e., with basic solvents. Equation (16) contains the difference in chemical solvation energies of the two anions, which will only be slightly affected by the dielectric permeability of the solvent. However, a decrease in dielectric permeability increases A_{mol} and thus increases K_T . Thus, improved titration conditions are achieved with basic solvents of high dielectric permeability and low ionic product.

A solvent which greatly improves the titration conditions should be characterized by a low K_{AM} and a relatively high K_{AMH^+} .

Titration conditions in amphoteric solvents are only improved for the titration of strong acids (hydrochloric) as the result of a decrease in the ionic product of the medium (case I a). Conditions are not improved for the titration of weak acids (case I b) in amphoteric solvents (Table 2).

For weak acids, such as benzoic, titration conditions can only be improved in basic solvents—amides, formamide, hydrazine, etc. The investigations of A. I. Shatenshtein [8] showed that it was possible to titrate benzamide, acetamide, and amino acids in liquid ammonia with a solution of sodamide in ammonia. Cundiff and Markunas [9] and Tomicek and Krepelka [10] were able to titrate very weak acids in pyridine, using the indicators hydrazobenzene and azoxybenzene. Fritz and Keen [11] and Dzyuba, Satanovskaya, and Izmailov [12] used dimethylformamide as a medium for the titration of such weak acids as phenols, sulfonamides, and barbituric acid derivatives. It is possible to titrate weak acids in ethylenediamine and its mixtures [13], and in mixtures of diethylamine, diethylformamide, pyridine, and hydrazine [14]. Pinkston and Briscoe [15] successfully titrated amphoteric substances in ethanolamine (case I c). Weak acids can be titrated in a mixture of ethylene glycol and chloroform [16].

In nearly all cases, the titrant used has been solution of sodium methylate in a mixture of methanol with benzene or with the basic solvent.

When the acids to be titrated are more soluble in nonaqueous solvents than in water, improved titration conditions are also achieved in amphoteric solvents. It is possible to determine the acidity of petroleum in nonaqueous solvents [17].

Case II. Improvement of Conditions for Titrating Bases. Reduction in K_T , the controlling factor for the titration of bases, depends on the ratio K_1^*/K_{NB} . It follows from (17) that K_T will decrease with a decrease in $K_{b(M-H)^-}$, or with an increase in the reciprocal of the dissociation constant of the solvent, K_{AM} , i.e., with a decrease in the basicity and an increase in the acidity of the solvent. As in the titration of acids, a reduction in the dielectric permeability of the solvent impairs the titration conditions, as a result of the increase in A_{mol} . Greater precision in the titration of weak organic bases can be achieved in acid solvents of high dielectric permeability and low ionic product. Acetic acid is mostly used as a medium for the titration of bases.

It follows from Table 3 that in acetic acid it is possible to titrate, with sufficient accuracy, even such weak bases as urea (K in water $10^{-13.8}$) or caffeine (K in water $10^{-13.4}$). Successful titrations have been achieved of weak aliphatic and aromatic bases, alkaloids, antibiotics, sulfonamides, etc. [18, 19, 20].

TABLE 1

Classification of Cases of Improvement of Titration Conditions in Nonaqueous Solvents

Case I	Case II
A decrease in the ratio K_1^*/K_{nA} is achieved in basic solvents for the titration of: a) Strong acids (decrease in K_1^*); b) very weak acids in basic solvent (K_{nA} is increased); c) amphoteric substances as acids in basic solvents ($K_1^*/K_{nA} \ll K_1^*/K_{nB}$).	A decrease in the ratio K_1^*/K_{nB} is achieved in solvents for the titration of: a) Strong bases (decrease in K_1^*); b) very weak bases (K_{nB} is increased); c) amphoteric substances as bases ($K_1^*/K_{nB} \ll K_1^*/K_{nA}$).
Case III	Case IV
There is a decrease in the ratio K_{nAII}/K_{nAI} in differentiating solvents for the titration of: a) Mixtures of mineral acids with strong organic acids; b) mixtures of organic acids of different types; c) mixtures of strong mineral acids; d) dibasic acids with respect to stepwise dissociation; e) salts of strong organic acids with respect to displacement of acid; f) mixtures of salts.	There is a decrease in the ratio K_{nBII}/K_{nBI} in differentiating solvents for the titration of: a) mixtures of mineral bases with strong organic bases; b) mixtures of organic bases of different types; c) mixtures of strong mineral bases; d) difunctional bases with respect to stepwise dissociation; e) salts of strong organic bases with respect to displacement of base; f) mixtures of salts.

TABLE 2

The Strengths of a Strong (hydrochloric) Acid and a Weak (benzoic) Acid in Solvents with Different Properties

Solvent	Dielectric permeability	Ionic product of medium pK_1	pK of benzoic acid	$-\log (K_1^*/K_{nA})$	pK of hydrochloric acid	$-\log (K_1^*/K_{nA})$
Ammonia	21.0	33.7	3.82	29.88	2.90	30.8
Water	78.5	14.0	4.02	9.89	0.80	13.2
Formamide	90.0	16.7	6.23	10.48	—	—
78% Dioxane	15.0	18.3	8.60	9.70	—	—
Acetonitrile	36.7	—	8.50	—	—	—
50% Acetone	24.0	20.3	9.80	10.50	2.47	17.83
Methanol	31.5	16.8	9.40	7.47	1.05	15.75
Ethanol	24.0	19.1	10.13	9.13	1.95	17.35
m-Cresol	18.0	14.5	10.29	4.16	—	—
Butanol	17.0	—	10.24	—	—	—
Acetone	19.1	—	11.95	—	4.00	—
Acetic acid	6.1	14.5	—	—	9.10	5.35

TABLE 3

The Strengths of Bases and their pK_t Values in Water, Acetic Acid and Formic Acid

Base	H ₂ O $pK_t = 14$		CH ₃ COOH $pK_t = 14.45$		HCOOH $pK_t = 5.7$	
	pK_B	$-\lg \frac{K_t^*}{K_{nB}}$	pK_B	$-\lg \frac{K_t^*}{K_{nB}}$	pK_B	$-\lg \frac{K_t^*}{K_{nB}}$
Diethylamine	2.9	11.1	—	—	0.74	5.0
Codeine	6.05	7.75	—	—	0.81	4.96
Morphine	6.13	7.87	—	—	0.84	4.93
Urea	13.82	0.18	10.24	4.2	1.25	4.50
Pyridine	8.69	5.31	6.1	8.35	0.95	5.3
Benzidine	9.03	3.97	—	—	0.75	5.0
Aniline	9.4	4.6	—	—	0.44	5.31
α -Naphthylamine	10.8	3.2	—	—	0.88	4.89
Caffeine	13.39	0.61	—	—	0.78	5.0
Theobromine	13.9	0.11	—	—	0.69	5.08
2,5-Dichloroaniline	—	—	9.48	4.97	—	—
Dimethylaminoazobenzene	—	—	8.32	8.13	—	—
Terphenylamine	—	—	5.38	9.07	—	—

It should be borne in mind that there is a large salt error [21] in titrations in acetic acid, because of its low dielectric permeability ($D = 6$). There has therefore been considerable interest in the use of formic acid ($D = 57$), particularly for the titration of very weak bases. But formic acid suffers from the disadvantage of a high ionic product ($K_t^* = 10^{-6}$), so that the range of change of pH in the titration is very small, and this decreases the precision of the titration [22]. Good results can be obtained with a mixture of acetic and formic acids [23], and with a mixture of acetic acid and its anhydride [24]; the latter reduces the ionic product and increases the acidity of the medium. Butyric [25] and propionic [26] acids have also been used together with acetic acid.

Shkodin, Izmailov, and Dzyuba [27] carried out titrations in monochloroacetic and trichloroacetic acids. M. I. Usanovich [28] successfully performed acid-base titrations in sulfuric acid. Bases in acetic acid and other acid solvents are usually titrated with perchloric acid. A detailed review of titrations in acid solvents is given by A. M. Shkodin [29]. There are good prospects for the use of hydrobromic acid and particularly of hydrofluoric acid ($D = 84$ at 0°) as solvents [30].

It is possible to determine the basic groups of amphoteric substances in acid solvents (case II c). Kilpi and his co-workers [31] have titrated amino acids in acetic acid. Nadeau and Branshen [32] have titrated alanine, cysteine, phenylalanine, cysteine, and other amino acids. Russel and Cameron [33] determined the number of basic groups in gelatine.

Improved conditions for titrating amphoteric substances can be attained in differentiating solvents [34]. A full analysis of amphoteric substances is possible by carrying out titrations in both acid and basic solvents [11].

Case III. Improvement of Conditions for Titrating Mixtures of Acids. The possibility of separate titration of mixed acids is determined by the ratio of their strengths, $K_t = K_{nAII} / K_{nAI}$. Literature data [6] shows that the ratio of the strengths of acids alters under the influence of many solvents, particularly of acids and differentiating solvents. The choice of solvents for titration should be made in the light of the experimental data. It follows from equation (18) that a change in the relative strengths of acids results from an increase in the difference between the chemical energies of solvation of the anions, $A_{x AII}^- - A_{x AI}^-$, and of the molecules, $A_{mol AII} - A_{mol AI}$, of the acids being titrated.

From equation (11) we obtain for the difference $A_{x AII}^- - A_{x AI}^-$:

$$A_{x AII}^- - A_{x AI}^- = \frac{e^2 N}{2} (1 - 1/D) \left(\frac{1}{r_2} - \frac{1}{r_1} \right) + \frac{e M N}{D} \times \left(\frac{n_2}{r_2^2} - \frac{n_1}{r_1^2} \right). \quad (20)$$

It follows from this expression that the greatest difference in energy will be attained in solvents of low dielectric constant with a high dipole moment. The change in A_{χ} is then greater, the greater is the localized charge on the acid anion. Usually the difference $A_{\chi_{AII}} - A_{\chi_{AI}}$ changes most when the anions formed from the acids are of different types. It has been shown that the change in the difference $A_{molII} - A_{molI}$ increases, if the solvent changes from one type to another, particularly if the acids compared belong to different chemical groups (differentiating action of solvent). In very acid solvents many weak acids do not give up a proton to the solvent, i.e., they do not show acid properties.

The greatest change in relative acid strengths will occur with a solvent which does not contain a hydroxyl group and is of low basicity, i.e., a differentiating solvent—ketones, nitriles, nitro compounds, and acids.

As an example of the change in the relative strengths of acids we show the effects of solvent on the ratios of the dissociation constants for hydrochloric and monochloroacetic acids, and for benzoic acid and 2,4-dinitrophenol (Table 4).

TABLE 4

The Differentiating Effects of Solvents on the Strengths of Acids.

Solvent	K_{n-HCl}	$K_{n-2, 6-dinitrophenol}$
	K_{n-CH_3COOH}	$K_{n-benzoic\ acid}$
Water	31.5	1.15
Formamide	—	50.0
Acetonitrile	—	80.0
Methanol	500 000.0	35.0
Ethanol	1500 000.0	33.0
Acetone	900 000.0	1500.0
Methyl ethyl ketone	1000 000.0	—
Dichloroethane	—	1600.0
Acetic acid	∞	—

Separate titrations in mixtures of strong mineral acids with weak organic acids (case III a) can often be achieved by using, as solvent, ketones, alcohols, mixtures of ketones with alcohols, and mixtures of alcohols or ketones with inert solvents [44]. The titration is usually performed with a solution of an alcoholate in the corresponding alcohol. Good results were obtained for the determination of small amounts of sulfuric acid as a contaminant in strong polybasic organic acids (citric, lactic, etc.) by titration in acetic acid, or in mixtures of this with acetic anhydride [24], and also in acetone [35]. Airs and Balfe [36] carried out separate conductometric titrations of mixtures of mineral and organic acids with phenol, in acetone and in acetone-water mixtures.

A number of papers have appeared on the separate titration of mixed organic acids (case III b). Separate titrations have been described of mixtures of carboxylic acids and phenols, of trichloroacetic and picric acids, and others, using acetone-water mixtures [37]. Separate titrations have been achieved in butanol [38, 39], acetone, and in mixtures of ketones with inert solvents. A separate titration was carried out in pyridine with a mixture of nitric, maleic, and acetic acids, and phenol [40]. Separate titrations of mixed organic acids has been achieved in dichloroethane, chlorobenzene, and benzene [41, 42].

Separate titrations of mixed mineral acids (case III c), for example-perchloric and hydrochloric, toluene-sulfonic and hydrochloric, have been carried out in acetic and trichloroacetic acids [43, 27]. The titration was performed with a solution of sodium acetate in an acid solvent.

The titration of dibasic acids by stepwise dissociation (case III d) is similar to the titration of acid mixtures. Maleic, phthalic, and succinic acids have been titrated in solution in ketones and in ketone-water mixtures [44], and in pyridine [40]. Titration of sulfuric acid in accordance with stepwise dissociation can be carried out in acetic acid.

The possibility of titrating salts by replacement (case III e) is determined, as in the titration of mixed acids, by the ratio of the dissociation constants of the replaced and titrant acids. The titration of salts of even strong organic acids can be carried out in butanol [39], acetone, and in mixtures of these solvents with water [45] and with methanol [1, 46]. In this case the titrant is a solution of hydrochloric or perchloric acid in the same solvent. Palit [47] showed that salts of organic acids could be titrated in glycols with inert solvents. Glycols mixed with alcohols have also been used [48]; salts of organic acids [49], as well as sulfates and halides, have been titrated in acetic acid and in mixtures of acetic acid with chloroform [50]. Perchloric acid in an acid solvent was used as titrant in the latter case. Mixtures of two or more salts can also be titrated by replacement [51]. Titration of salts by replacement in propionic acid has been described [52].

Case IV. The Separate Titration of Mixtures of Bases. The possibility of titrating mixtures of bases separately is governed by the ratio of their dissociation constants, $K_t = K_{nBII} / K_{nBI}$. Since K_{b_2} and K_{b_1} do not depend on the solvent, any increase in the difference between the constants is determined, as in the titration of acid mixtures, by the changes in the differences $A_{xBIIH^+} - A_{xBIH^+}$ and $A_{moIBII} - A_{moIBI}$. Varied and considerable changes in these differences can be obtained by the use of differentiating solvents, particularly if the bases to be titrated are of different chemical types. The value of A_x changes more, the more localized is the charge on the cation. The value of $A_{moIBII} - A_{moIBI}$ alters appreciably when the bases form compounds of different composition with the solvent molecules.

The difference $A_{xBIIH^+} - A_{xBIH^+}$ is determined by an equation similar to (11), and consequently increases with decreasing dielectric permeability. Thus, improved conditions for the separate titration of bases are achieved in media which do not contain hydroxyl groups and have low dielectric permeability, i.e., differentiating solvents. In addition to these general considerations it is desirable to make use of any experimental data as to the dissociation constants of the bases and the nonaqueous solvents [53]. Titration of mixed bases is classified under the same subgroups as for the titration of mixed acids.

Mixed mineral and organic bases (case IV a), such as potassium acetate, butylamine, and pyridine, can be titrated separately in a 10 : 1 mixture of chloroform and acetic acid, using perchloric acid in dioxane as titrant [54]. Separate titrations of mixed sodium benzoate and caffeine, and also of mixed sodium salicylate and caffeine, have been carried out in a mixture of acetic acid with benzene [1, 55].

Mixed organic bases (case IV b), such as pyridine and dibutylamine, aniline and chloroaniline, and pyridine and caffeine, have been titrated separately in acetonitrile [56]. The titrant was a solution of perchloric acid in dioxane. Pifer, Wollisch, and Schmall [54] titrated pyridine and butylamine separately in a 10 : 1 mixture of chloroform and acetic acid, using the same titrant as above.

Separate titrations of mixed mineral bases (case IV c) were achieved by Pifer, Wollisch, and Schmall [57] in a 10 : 1 mixture of chloroform and acetic acid. Separate titrations of K^+ and NH_4^+ ions were carried out in the presence of one of the following— Li^+ , Na^+ , Ca^{2+} , Ba^{2+} , Ag^+ , Cd^{2+} , and Zn^{2+} .

The titration of difunctional bases in accordance with their stepwise dissociation (case IV d) has been performed with quinine, esterol and other organic bases in solution in chloroform, dioxane, and ethyl acetate, with perchloric acid in dioxane as titrant [57].

Titration of salts of organic bases by displacement (case IV e) has been applied mainly to alkaloids in solution in alcohols and ketones, with sodium ethylate as titrant [34, 58]. Izmailov and Dzyuba [1] titrated salts of Li, Na, Ca, and Ba in a mixture of acetic acid and benzene, with potassium acetate in acetic acid as titrant.

Titration of mixed acids, and of salts by displacement of acid, is usually carried out potentiometrically, using glass or quinhydrone electrodes. Glass and antimony electrodes are used for the titration of mixed bases, and of salts by displacement of the base.

The Properties of Indicators and Indicator Electrodes in Nonaqueous Solvents

The same methods are used for determining titration end points in nonaqueous solutions as in water. Usually the improvement of the titration conditions is so great in nonaqueous solution that the end points can always be determined with indicators [59]. It is only necessary to use potentiometric titrations in some cases of the separate titrations of mixed acids or bases and of the titration of salts by displacement.

TABLE 5

Dissociation Constant Indices of Some Colored Indicators in Water, Nonaqueous, and Mixed Solvents

Indicator	Solvent						
	water	meth- anol	etha- nol	bu- tanol	50% acetone- water	90% acetone- water	acetone
Methyl yellow	3.25	3.3	3.10	3.0	2.7	2.4	2.2
Methyl orange	3.45	3.8	3.4	3.3	3.0	2.4	2.5
Bromophenol blue	4.1	8.9	9.6	9.1	5.2	7.4	10.1
Bromocresol green	4.9	9.8	10.65	10.4	6.0	8.5	10.8
Bromocresol purple	6.4	11.3	12.05	10.7	7.6	10.25	13.25
Bromothymol blue	7.2	12.4	13.2	13.0	8.5	11.6	14.3
Neutral red	7.4	8.2	8.2	8.3	6.9	6.0	5.4
Phenol red	8.0	12.8	13.55	14.0	9.4	12.1	—

It should be borne in mind that dissociation constants of titrants do not change in the same way as do those indicator acids and bases. It is therefore necessary to select indicators on the basis of experimental data as to their dissociation constants or range of color change in nonaqueous solvents. The behavior of many indicators has now been investigated in a number of nonaqueous solvents [1]. Table 5 shows some dissociation constant indices for indicators in amphoteric and some differentiating solvents, which were obtained in our laboratory [60]. These constants characterize the range of change of indicator, expressed in terms of the specific acidity scale pH_p . The basis of this scale for any solvent is a solution of lyonium ion, MH^+ , in the given solvent, with an activity equal to one [1, 61]:

$$\text{pH}_p = -\lg a_{\text{MH}^+} = -\lg C_{\text{MH}^+} - \lg \gamma_{\text{MH}^+}^*, \quad (21)$$

where $\gamma_{\text{MH}^+}^*$ is the concentration activity coefficient of the lyonium ion. Fluorescent indicators have also been investigated in these solvents [62].

The behavior of an indicator in an acid or basic solvent of low dielectric permeability depends on the titrant, as well as on the medium. Table 6 shows some indicators recommended by Ekeblad and Erne [63] for titrations in the basic solvents dimethylformamide, benzylamine, pyridine, and ethylenediamine, and some others recommended by Wichtl [64] for titrations in acetic acid. The latter can also be used in other acid solvents.

The use of the hydrogen electrode in nonaqueous solvents is affected by the same restrictions as in water, with the added restriction of the reducing action of hydrogen and platinum black on the solvent itself. It is therefore rather better to use a gold electrode covered with platinum black [1].

The use of quinhydrone electrodes is possible in the acid solvents formic, acetic, and other acids. In amphoteric electrolytes—alcohols, ketones, nitriles, and their mixtures with water or with inert solvents—the quinhydrone electrode can only be used, as in water, for acid solutions [1, 65]; it is not applicable to basic solvents, or in the presence of strong oxidizing or reducing agents. Quinhydrone is considerably more soluble in organic nonaqueous solvents than in water, so that it is not necessary to use saturated solutions.

The use of antimony and other metal-oxide electrodes is restricted in acid solvents, in water [66], and in amphoteric solvents [67], because there is a discontinuity in the potential-pH curve in the region of neutral solutions. There are no such complications in the use of this electrode for titration in the basic solvents: alkyl- and dialkyl-formamides, aliphatic and aromatic amines, pyridine, and their mixtures with inert solvents. As in water, the application of the antimony electrode is restricted by the effects of complex-formers and of oxidizing and reducing agents.

There are a number of restrictions on the use of the glass electrode for titrations in nonaqueous solvents [1]. The cationic function of the electrode increases in basic solvents, and errors arise at lower values of pH_p . In acid

TABLE 6

Scale of Indicators for Basic and Acid Solvents

Indicator	Color in alkaline region	Color in acid region
	Basic solvents	
Thymol Blue	Yellow	Red
Thymolphthalein	Yellow	Red
Phenolphthalein	Red	Colorless
Azo Violet	Rose	Violet
o-Nitroaniline	Orange	Yellow
	Acid solvents	
Crystal Violet	Blue-green	Yellow
Malachite Green	Green	Yellow
α -Naphtholbenzein	Yellow	Green
Benzoylauramine	Blue-green	Yellow
Scarlet Red (Sudan III)	Blue violet	Blue
Neutral Red	Red	Blue
N. I. Sulfate Blue	Blue	Red
BZL Anthraquinone Blue	Blue	Red

solvents the anionic function of the electrode is increased, and errors arise at higher values of pH_p [1]. Also, electrodes made from MacInnes and Dole glass, or from Hughes glass, cannot be used with acid and basic solvents. The glass electrode is applicable for titrations in amphoteric solvents, and in their mixtures with water and with inert solvents. But all the "alkaline" and "acid" errors occur at lower values of pH_p in these solvents than in water. Considerably less "alkaline" error was observed with Perley type glass [68].

In nonaqueous solvents, as in water, it is possible to carry out differential titrations, titration to a "jump", etc.

Aqueous reference electrodes (calomel, silver-silver chloride) are mostly used, since the junction potential at the water-nonaqueous solvent boundary alters little during the titration, but it is necessary to prevent interdiffusion of the two liquids.

If it is essential to use only the one nonaqueous solvent throughout, then the reference electrode can consist of an indicator electrode immersed in a buffer solution made up in the same solvent.

In titrations in amphoteric and acid solvents it is permissible to use silver-silver halide and calomel electrodes, connected by a solution of halide which is readily soluble in the solvent used [69].

Prospects for the Use of Nonaqueous Solvents in Volumetric Analysis

Titration in nonaqueous solvents have now been carried out for examples of all the above types of classification. Nonaqueous solvents considerably improve the conditions for acid-base titrations, and it is possible to titrate very weak acids and bases, amphoteric substances, and even substances which are neutral in water. It is also possible to titrate mixed acids and bases separately when they have nearly the same dissociation constants, and to titrate salts of weak acids by displacement of the acid, and salts of weak bases by displacement of the base. There are number of reviews of titrations in nonaqueous solvents [1, 70].

The development of theoretical and experimental investigation of nonaqueous solvents has been accompanied by the accumulation of data on the strengths of acids and bases, and on the properties of indicators and indicator electrodes in these media, and on their ionic products. This data makes possible a correct choice of solvent and titration conditions for various purposes. However, the information available is still inadequate, and it may be necessary to chose a solvent by analogy with a titration which has already been investigated.

Acid-base titration is now being applied to complex materials, such as heteroorganic compounds [71], complex derivatives, vegetable mixtures [72], etc. There have been improvements in the conditions for indirect acid-base titrations, as for the determination of aldehydes, ketones, and acetylene derivatives [73-76].

The use of nonaqueous solvents changes not only the strengths of acids and bases, but also the strengths of salts, and other properties of electrolytes, such as solubilities and the values of several electrode potentials, including oxidation-reduction potentials [1]. All these changes can be used to improve the conditions for the corresponding applications of volumetric analysis.

The effects of solvent on the solubility and strength of salts enables us to extend the range of precipitation titrations [77], by applying this method to the determination of salts which are comparatively soluble in water, but very sparingly soluble in nonaqueous solvents. The differentiating action of solvents on the strengths of salts [78] can be utilized for the separate precipitation titration of mixed salts with a common cation or anion, as in the separate titration of two bromides [79].

The effects of solvents on oxidation-reduction potentials enable us, in many cases, to improve the conditions for oxidimetric and reductimetric titrations. A number of oxidation-reduction titrations of inorganic and organic substances have been carried out by Tomicek and his co-workers [80] in glacial acetic acid. Minchevskii [81] established the conditions for titrating uranium in a mixture of ethyl acetate and ethyl ether, and for determining copper, vanadium, and molybdenum in nonaqueous solvents by titration with chromous acetate solution.

Thus, the prospect is that nonaqueous solvents will be used in the future, not only for acid-base titrations, but also for other types of volumetric analysis.

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