

Acid–Base Titrations in Nonaqueous Solvents and Solvent Mixtures

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The use of nonaqueous solvents has many advantages in analytical chemistry, especially in acid–base titrations (1–5). The number of methods based on redox reactions in nonaqueous solutions (2, 4) is negligible relative to that of acid–base determinations, and the chelatometric titrations (e.g., those of metal ions in dimethylformamide with EDTA; ref 5) are of little practical importance.

Since several organic bases and acids (as well as their salts) can be found in pharmaceuticals, nonaqueous titrations are generally used for their determination. These methods are some of the most popular quantitative pharmaceutical analyses. The determination of these substances by nonaqueous titrations is highly preferred in different pharmacopoeias since the method is quantitative, exact, and reproducible. There are over a hundred assays based on this method in the *European Pharmacopoeia 2000* (6) and a similar order of magnitude can be estimated in *USP 24* (7) (in spite of the fact that HPLC and similar methods are sometimes preferred).

At the same time, the interpretation of these reactions is rather inconsistent; the theories and suppositions of the 1920s and 1930s are applied and sometimes confused. For example, one of the most popular textbooks on analytical chemistry (8) discusses the topics of nonaqueous media on the grounds of the so-called solvent theory. As it will be treated in this paper, this theory can be easily understood, explains the promoting (and leveling) effects, but is not applicable to the differentiating effect. The following discussion tries to address these issues.

Background

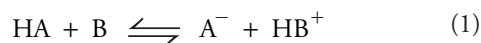
The concept of acids and bases is relatively old. Their connection to special materials and the study of their aqueous solutions was established during the 19th century. The theory, attributed generally to Arrhenius, differentiates between acids and bases well, but it is insufficient for nitrogen-bases or salts producing acidic or basic solutions. (The auxiliary idea of “hydrolysis” for these kind of interactions has been a troublesome one until now.)

The year 1923 was a very important year for chemical sciences, especially for the physical chemistry of solutions. The “Theory of Electrolytes” published in 1923 by P. Debye and E. Hückel (9) was tremendously successful. Physical-chemical research was influenced by their theory for a long time. Some researchers thought that all phenomena experienced in solution could be explained by the electrostatic interactions of the ions, and there was no need to assume other specific interactions. Coordination-chemistry research, while started earlier, came to a standstill, and this stop can be also considered as a consequence of the Debye–Hückel theory (10). (Coordination-chemistry research was reinvigorated nearly two decades later after the excellent dissertation of J. Bjerrum; ref 11)

The paper of J. N. Brønsted on “The Conception of Acids and Bases” (12) was also published in 1923, as well as T. M. Lowry’s work about the “Uniqueness of Hydrogen” (13). The basis for the Brønsted–Lowry theory was laid in these publications. Considering further developments, Brønsted’s concept was proven more useful in analytical chemistry for the explanation of acid–base reactions.

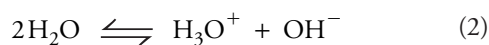
Brønsted’s Acid–Base Theory

The essence of an acid–base reaction is the transfer of a proton from the acid, HA, to a base, B, in an equilibrium reaction, where a new acid and a new base are formed



Pairs HA, A[−] and B, BH⁺ are coupled by the transfer of a proton and are called conjugate (connected or corresponding) acid–base pairs. Equation 1 gives a common description for any species producing an acidic or basic aqueous solution (independent of whether the species was a compound or an ion) since water is able to react either as an acid or as a base (i.e., it can act both as HA or B, depending on the properties of the partner).

Brønsted’s theory perfectly describes the fact that water can form two conjugate acid–base pairs: the H₂O, OH[−] and H₃O⁺, H₂O. The H₃O⁺ and OH[−] species represent the strongest possible acid and base in aqueous solutions and characterize acid–base reactions in the water. The autoprotolysis of water (or its autodissociation),



describes the ionic product of water

$$K_{\text{W}} = [\text{H}_3\text{O}^+][\text{OH}^-] \quad (3)$$

(the [H₂O] can be taken as constant) and the concept of pH, as well as the well-known connection of dissociation constants of conjugated acid–base pairs

$$\begin{aligned} K_{\text{A}} \times K_{\text{B}} &= \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} \times \frac{[\text{OH}^-][\text{HA}]}{[\text{A}^-]} \\ &= [\text{H}_3\text{O}^+][\text{OH}^-] = K_{\text{W}} (= K_{\text{ip}}) \end{aligned} \quad (4)$$

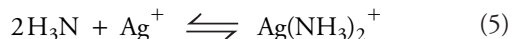
where K_{W} is the ion-product constant (K_{ip}) of water.

Lewis’ Acid–Base Theory

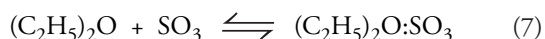
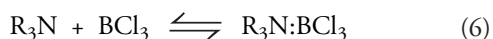
Lewis’ booklet, *Valence and Structure of Atoms and Molecules* (14), where Lewis’ acid–base concept was first outlined, was also published in 1923 (15). The central idea of Lewis’ theory is that the base is able to donate its free electron pair

to the acid, which possesses free electron orbitals of appropriate energy level.

This concept can be used for complex-formation reactions, where the electron-pair donor, the ligand, forms a coordinate covalent bond with the acid, the electron-pair acceptor. For example,



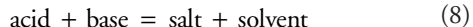
Similarly, this concept helps in understanding some acid–base reactions in aprotic nonaqueous solutions, for example



It is clear that electron pair donor–acceptor complexes are formed; that is, eqs 6 and 7 characterize typical Lewis' acid–base reactions. Based on reactions of this kind, the expressions of Lewis acids and bases are generally used and contrasted with Brønsted acids and bases. This difference can be important since, for example, HCl is not a Lewis acid because the covalent molecule has no empty orbital while all metals and electron-deficient compounds are (on the other hand, most of the latter ones are not Brønsted acids, etc.).

The Solvent (Autodissociation) Theory

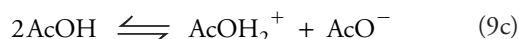
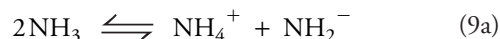
The third often used acid–base theory, the solvent theory, is not directly connected to the year 1923, since it was introduced by Kraus in 1922 (16). The basic equation can be described as,



which was formulated by Franklin (17) in 1924. This theory is a return to Arrhenius' concept, and actually originated from the earlier works of P. Walden, with the details being summarized in 1924 (18).

The theory is more complex than shown by eq 8, and can be understood using the analogy of water. The autoprotolysis (or autodissociation) of water (see eqs 2 and 3) is

extrapolated for other solvents (5, 19), for example,

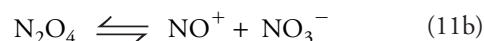
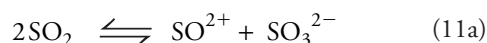


where Me stands for methyl, CH_3^- , and Ac for acetyl, CH_3CO^- group. The values of $\log K_{\text{ip}}$ are -32.7 ($T = -33^\circ\text{C}$; eq 9a), -16.9 (eq 9b), and -14.45 (eq 9c). These three examples can be accepted, but similar extrapolation gives very doubtful results, as in the case of dimethyl sulfoxide (DMSO),



Various $\log K_{\text{ip}}$ values are found in the literature: -33.3 (5) and -17.3 (19). Further examples also exist, like those of formamides, ketones, dioxane, and so forth (2, 19). It seems that these values are extremely influenced, or even determined, by the purity of the solvent (especially by its water content), and therefore they can and must be used only with great care.

All examples cited so far concern solvent molecules containing hydrogen, but only those in eqs 9a–c have both proton-donor and proton-acceptor abilities, while DMSO is only a proton acceptor (not according to eq 10, because this molecule has no “active” hydrogen). It is clear that the solvent theory is less suitable in such cases, unless the reactants are extremely aggressive. But the solvent theory is well applicable for solvents having no hydrogen, such as liquid SO_2 or NO_2 ,



since Na_2SO_3 is really a base in liquid SO_2 or NOCl is an acid in liquid N_2O_4 .

Table 1. Brønsted's Classification of the Solvents

Class	Property ^a	Examples	
		High ϵ_r	Low ϵ_r
Protogenic (acidic)	HA	HF, H_2SO_4	CH_3COOH (HCOOH) (CHCl_3)
Protophilic (basic)	B	$\text{Me}_4\text{-carbamide}$	amines, pyridine (ketones)
Amphiprotic	HA and B	H_2O , MeOH	alcohols
Aprotic	N	(MeCN , MeNO_2)	hydrocarbons (benzene, CS_2)

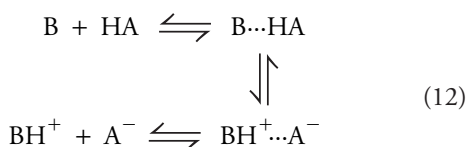
^aHA = proton donor; B = proton acceptor; N = neutral.

The Central Role of Hydrogen Bonding in Acid–Base Reactions

Brønsted's classification of solvents (20), published some years after 1923, strictly differentiates the solvents in eqs 10 and 11 and those of eqs 9a–c. In this very useful classification, 9a (ammonia) is a nice example of protophilic solvent; 9b (MeOH) is a typical amphiprotic, while 9c (AcOH) is the most used protogenic example. All other examples, in spite of eq 10, belong in the group of aprotic solvents. The next step in Brønsted's solvent classification is the formation of two subdivisions: the group of solvents of high relative permittivity (ϵ_r ; also called the dielectric constant) and that of low relative permittivity (see Table 1).

The original Brønsted concept of 1923 (12) itself can be used for solving most problems of nonaqueous analytical chemistry. The central species in this theory is the hydrogen (ion), as in the concept of hydrogen bonding, but the connections were not realized at that time. This is surprising enough, as one of the best definition of H-bonding was known at the time, referring to the connection between the structure and properties of water: "...a free pair of electrons on one water molecule might be able to exert sufficient force on a hydrogen held by a pair of electrons on another water molecule to bind the two molecules together..." (21).

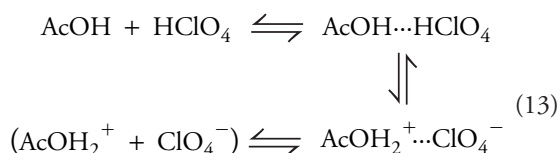
Several years passed before the monograph of Pimentel and McClellan on H-bonding was published (22) and the general mechanism of proton donation (acid–base reaction) was first formulated,



where \cdots denotes a H-bond. It follows, that $\text{B} \cdots \text{HA}$ means the common H-bonded complex, while $\text{BH}^+ \cdots \text{A}^-$ is the symbol of a H-bonded ion pair.

Equation 1 is a typical Brønsted equation, but it is actually the extremities of eq 12, since it neglects the H-bonded species and assumes complete dissociation. This assumption is valid only when the solvent is of high relative permittivity, as in the water model. However, most solvents used in nonaqueous practice have lower relative permittivities (Table 2) and therefore the H-bridged ion pairs remain generally undissociated.

For demonstrating the consequences, a well-known example can be cited—the dissolution of perchloric acid in glacial acetic acid (the general titrant for bases). In this case, acetic acid has to accept the unusual duty of a base



If only the initial and final (ionized) states were considered (the assumed concentrations of acetonium and perchlorate ions were measured by conductometry), the "dissociation constant" of perchloric acid could also be calculated in this

Table 2. Relative Permittivities of Some Important Solvents at 25 °C

Solvent	ϵ_r	Solvent	ϵ_r
water	78.54	N-methylformamide	182.4
methanol	32.63	dimethylformamide	36.71
ethanol	24.53		
ethylene glycol	37.7	acetic anhydride	22.1
phenol (60 °C)	9.8	nitromethane	35.87
		nitrobenzene	34.82
formic acid	58.5		
acetic acid	6.13	acetone	20.7
propionic acid	3.44	methylisobutyl ketone	12.92
		dioxane	2.27
ethylenediamine	14.2		
n-butylamine	4.88	chloroform	4.81
ammonia (−33 °C)	22.4	carbon tetrachloride	2.23
pyridine	12.4	benzene	2.27
acetonitrile	36.2	n-hexane	1.9

NOTE: See ref 5 and 17.

solvent (19) as

$$K_A = \frac{[\text{AcOH}_2^+][\text{ClO}_4^-]}{[\text{HClO}_4]} = 10^{-4.85} \quad (14)$$

and the picture is in agreement with eq 9c of solvent theory. The result, however, is inconsistent with practical experiences. The K_A value in eq 14 is characteristic for a weak acid (in aqueous solution), in contrast to the fact that perchloric acid is actually a very strong acid in glacial acetic acid (1–5, 19). The explanation is that the relative permittivity of glacial acetic acid is very low (as demonstrated in Table 2), therefore the H-bonded ion pair $\text{AcOH}_2^+ \cdots \text{ClO}_4^-$ virtually does not dissociate but this species represents, in itself, a strong acid.

The simplicity of solvent (or autoprotolysis) theory thus causes confusion and this is the reason why the expressions, used for characterizing the nonaqueous equilibria, are incoherent (especially when the effect of solvolysis is included). On this basis, the critical summary of Kolthoff and Bruckenstein (1) can be regarded as authoritative.

Our survey may start with the equilibria demonstrated by eq 12. The solvent molecules can act either as HA or as B. The interaction of an acid with a basic (protophilic) solvent is discussed first. Based on the first equilibrium of eq 12, the formation constant (K_{form}) of a H-bonded complex ($\text{B} \cdots \text{HA}$) can be defined. Its value is generally unknown, nevertheless the solvent is in great excess and therefore $[\text{B}]$ is practically constant (like $[\text{H}_2\text{O}]$ in eq 3). It follows that $[\text{B} \cdots \text{HA}]$ is directly proportional to $[\text{HA}]$. The second equilibrium characterizes the formation of a H-bonded ion pair, $\text{BH}^+ \cdots \text{A}^-$, and this constant can be designated as K_{ion} . The "dissociation constant", K_{diss} , refers only to the last equilibrium of eq 12, that is, to the ionic dissociation of the H-bonded ion pair. Following Kolthoff and Bruckenstein (1),

we can define the “overall” constant as

$$K_{\text{overall}} = \frac{[\text{BH}^+][\text{A}^-]}{[\text{HA}] + [\text{B} \cdots \text{HA}] + [\text{BH}^+ \cdots \text{A}^-]} \quad (15)$$

$$= \frac{K_{\text{form}} \times K_{\text{ion}} \times K_{\text{diss}}}{1 + K_{\text{form}} + K_{\text{form}} \times K_{\text{ion}}}$$

Note that this constant differs fundamentally from the common meaning of an acid dissociation constant, K_{A} , as used in eq 4. The denominator of this expression represents the total concentration of the dissolved acid.

If the K_{form} is very large (i.e., the total quantity of HA is assumed to be bound as 1:1 solvate) (1–5, 18) then eq 15 can be approximated as

$$K_{\text{overall}} = \frac{[\text{BH}^+][\text{A}^-]}{[\text{B} \cdots \text{HA}] + [\text{BH}^+ \cdots \text{A}^-]} = \frac{K_{\text{ion}} \times K_{\text{diss}}}{1 + K_{\text{ion}}} \quad (16)$$

Similar results can be deduced for the solutions of bases in acidic (protogenic) solvents. In this case, HA is in great excess and its concentration can be regarded as constant. It follows that this value can be incorporated into K_{form} and K_{overall} .

Obviously, not only a 1:1 solvate is formed in the solute–solvent interactions, but there are possibilities also for solute–solute associations, et cetera and therefore we will not go into the further details of the mathematical background. (However, it is worth mentioning that the interactions of Lewis acids and bases can be discussed similarly.)

According to these considerations, the relative permittivity of the solvent is of great importance in nonaqueous acid–base reactions. When only the BH^+ and A^- state is considered as the result of the acid–base reaction, the equilibrium con-

stant (K_{overall} , eq 16) can be high only when K_{diss} is high, that is when the relative permittivity of the solvent is high. (The relative permittivities of some more important solvents are collected in Table 2. It is worth mentioning that $\epsilon_{\text{r}} = 30$ was recommended (19) as a distinction between “polar” and “apolar” solvents.) So the low permittivity would be a contradiction to the experimental applicability of acid–base titrations in glacial acetic acid, but glacial acetic acid is one of the best solvents for nonaqueous titration of organic bases.

However, the formation of the H-bonded ion pair implies that the acid–base reaction has already occurred (as it can be proved by some acid–base indicators like dimethylamino azobenzene; ref 23). Equation 16 has to be modified as

$$K_{\text{overall}}^* = \frac{[\text{BH}^+][\text{A}^-] + [\text{BH}^+ \cdots \text{A}^-]}{[\text{HA}] + [\text{B} \cdots \text{HA}]} \equiv K_{\text{ion}}(1 + K_{\text{diss}}) \quad (17)$$

and K_{overall}^* defined this way can have a high value even in solutions of low ϵ_{r} , in agreement with the experimental facts.

The considerations, begun with eq 12, outline the H-bond concept of nonaqueous acid–base reactions. For presenting the differences and connections between the states of a H-bonded complex ($\text{B} \cdots \text{HA}$) and a H-bonded ion pair ($\text{BH}^+ \cdots \text{A}^-$), two linear H-bridged systems containing N and O pillar atoms can be chosen (although the bond angle of 180° is quite rare, the conclusions are not influenced by the simplifications). The first example is the interaction between two $-\text{C}(\text{O})\text{NH}-$ groups (which is the basic unit in the H-bonded structure of proteins). In this H-bond, the amide group is the proton donor and the carbonyl group is the proton acceptor. The second example can be the H-bridge between acetic acid (as proton donor) and a nitrogen base as proton acceptor (the system that occurs most often in non-

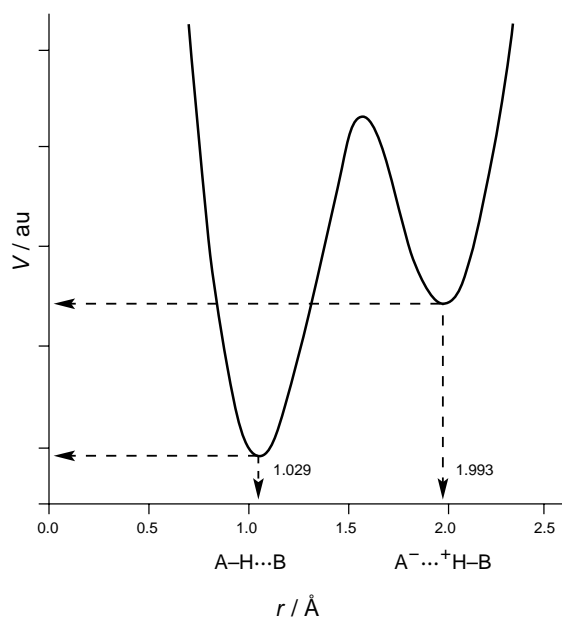


Figure 1. The change of the potential energy as a function of atomic distances in the interaction between two $-\text{C}(\text{O})\text{NH}-$ groups, which is the basic unit in the H-bonded structure of proteins.

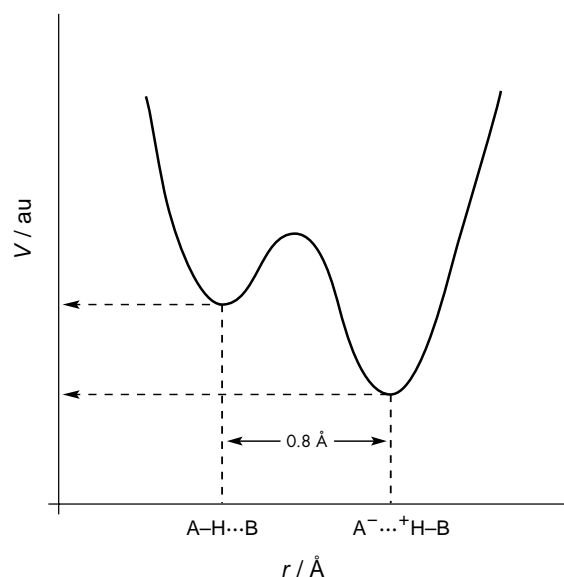


Figure 2. The change of the potential energy as a function of atomic distances in the interaction between acetic acid and a nitrogen base, $-\text{OH} \cdots \text{N} \equiv$, the system which occurs most often in nonaqueous titrations.

aqueous titrations). The potential energy function can be calculated using different methods (24, 25), but graphical representation always gives the pictures presented in Figures 1 and 2. (It can be mentioned that some rare species also exist having so-called strong H-bonds with particular properties, but no examples are known in analytical chemistry.)

The covalent bond between N and H (Figure 1) remains in the amide group, though somewhat elongated, and the proton stays mostly here, because this status gives the minimum in potential energy of the H-bond. Since the potential energy for H in the second minimum (nearer to the carbonyl oxygen) is higher, the H...O distance is longer (this group is practically unprotonated). In the second case (Figure 2) the potential energy is lower in the second minimum, and the proton prefers the nitrogen and practically shifts to it producing ammonium type ion and N-H⁺ covalent bond while the H-bonding between the pillar atoms (O and N) remains. This means that the original functions are changed in the acid-base system, thereupon starting with ⁺HN≡ proton donor and AcO⁻ proton acceptor, the representation of the potential energy should give the same result as Figure 1.

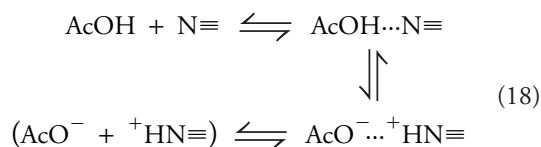
The AcOH-HClO₄ interaction (O...HO H-bonding) can be discussed identically. Since the electron densities of the two oxygens are different and that of the perchlorate ion is lower (ClO₄⁻ is known to be extremely weak base), the AcOH₂⁺...ClO₄⁻ H-bonded ion pair is really the strongest acid possible in glacial acetic acid.

Considering the nonaqueous titrations as interactions among H-bridged systems and accepting the assumption that the central step in an acid-base reaction is the transformation of H-bonded complex into a H-bonded ion pair (which can be generalized as the formation of an ion pair), the different effects can be well understood.

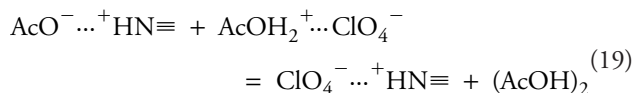
Promoting (and Leveling) Effects

Since the N≡ group of a base is usually a stronger proton acceptor than any oxygen of carboxylate group, and -COOH is stronger proton donor than H₂O, the protons are more shifted in the H-bridge to the base in glacial acetic acid than in water (in spite of the fact that the degree of dissociation is lower). Clearly, glacial acetic acid is a *promoting solvent* for most bases. It follows similarly that the strong proton donating solvent is not able to make differences among the (relatively strong) bases: promoting solvents generally show *leveling effects*, too.

Using eq 12 for glacial acetic acid and a N-base:



and combining it with eq 13, the equation of the base titration can be simply written:

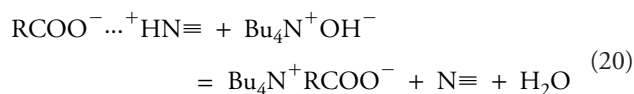


It must be recognized that this equation is formally identical

with eq 8, and (AcOH)₂ symbolizes the unit of the solvent, the dimeric acetic acid molecule (Figure 3).

As protogenic solvents are both promoting and leveling for bases, the protophilic solvents (e.g., pyridine, ethylenediamine, *n*-butylamine) promote and level similarly the strengths of dissolved acids. Denoting these basic solvents as N≡ and substituting Ac with a general RCO (acyl) symbol, eq 17 can be accepted as the demonstration of promoting (and leveling) effect of proton accepting solvents on acids, too.

Since tetrabutylammonium hydroxide (TBAH), which is a strong base of ion pair character, is preferred in protophilic solvents as titrant, the general equation for the titration of organic acids (RCOOH) in protophilic solvents (N≡) can be also written rather simply

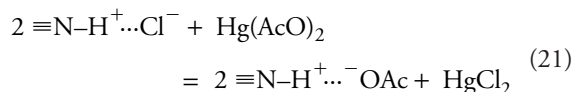


Differentiating Effect

Both the parallel promoting and leveling effects of the most important nonaqueous solvents can nicely be explained as outlined above, but some additional considerations are necessary to interpret the third effect, *differentiating*, which means the possibility of separate consecutive titrations of acids—or bases, respectively—in the presence of each other. As in the first approach, the effect of basic solvents on bases and that of acidic solvents on acids could be examined (although no analytical uses exist). It seems clear that only bases having stronger basicity than the solvent molecules are able to act as bases in basic (protophilic) solvents. Reacting with any acid, these proton acceptor bases bind the oscillating proton better and longer in H-bonded ion pair form (Figure 2) than the solvent molecules themselves. Since the pillar atoms in the H-bonded ion pairs are often identical, the “stronger basicity” is the effect of the whole molecule concentrated on the given pillar atom. It follows, that the *individual properties* of the molecule are expressed in differentiation, therefore milder specific solvation seems to be more advantageous.

The case of acids in typical acidic solvents is different, since these solvents have their own characteristic structures, for example, acetic acid is known to exist in a stable dimeric form (Figure 3). When dissolving any carboxylic acid in glacial acetic acid, similar cycles are formed between the carboxylic groups with double H-bondings and these species have no acidic character. (The organic acid salts can be titrated similarly as pure bases.)

Among the inorganic acids, nitric and hydrochloric acids are *acids* in glacial acetic acid (although weaker than perchloric acid) but sulfuric and phosphoric acids are only monobasic ones. The hydrochloric salts are most interesting in practice. Using the fact that neither mercuric acetate nor mercuric chloride dissociate in glacial acetic acid, the chloride (of a hydrochloride salt) can be exchanged for acetate easily



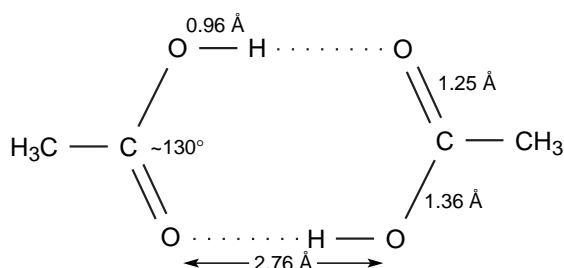


Figure 3. Schematic representation of the cyclic structure of dimeric acetic acid.

and the acetate formed can be titrated directly (eq 18). The elegant solution is overshadowed by the mercury pollution of the environment. Consequently, the H-bonded interactions are in the center of the differentiating effect, too, but no strong (i.e., promoting) proton donor or acceptor solvents can be used since the individual properties of the molecule must not be hindered (leveled).

It is not surprising that the most recommended solvents for differential titration of bases are weak proton donor ("acidic") solvents, such as chloroform, alcohols, et cetera, which really do not promote the basicity but only the manifestation of the intrinsic differences. Similarly, weak proton accepting solvents (like ketones) are used to differentiate the acids. Most likely, methyl isobutyl ketone is the best known example, since five acids (perchloric, hydrochloric, salicylic, and acetic acid as well as phenol) can be titrated in it with TBAH titrant, using potentiometric end point determination (26). Acetonitrile (CH_3CN , a solvent of relative high ϵ_r) is proposed for both purposes. Unfortunately, the acid-base equilibria are rather complicated, since the solvated proton reacts very slowly, the anions are poorly solvated and, therefore, unknown associates can be formed.

For differential titrations, the so-called G-H mixtures are highly preferred, where G refers to a glycol (mostly ethylene glycol, but sometimes phenol) and H is an aprotic inert hydrocarbon (*n*-hexane or benzene, but sometimes chloroform or CCl_4). The H component serves especially for dissolving the sample. Since the G molecule, as proton donor, forms H-bonded complexes or ion pairs in equilibria with the solutes (with bases or with the anion part of the acids), the similar components are differentiated and can be titrated successively.

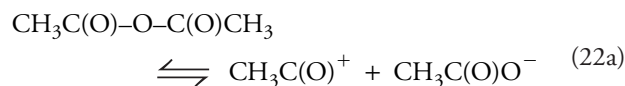
To demonstrate the role of G component, it may be worth mentioning that ClO_4^- ion and pyrocatechol form H-bonded complexes of $K = 20.6$ (in nitrobenzene, an inert solvent of high ϵ_r), the similar formation constant is 4.40 in phenol, 3.04 in ethylene glycol and 0.36 in ethanol, respectively (27). Some other stability constants for H-bridged anion-pyrocatechol complexes in nitromethane at 37 °C: Cl^- , 418; Br^- , 187; I^- , 27.8; ClO_4^- , 11.2 (28). In spite of the fact, that the values are low, they can be well paralleled with the solvating abilities of glycols against anions.

Formic Acid and Acetic Anhydride as Solvents

Although we do not intend to give a complete survey, the increasing uses of formic acid (HCOOH) and acetic anhydride (Ac_2O : $\text{CH}_3\text{C}(\text{O})-\text{O}-\text{C}(\text{O})\text{CH}_3$) in titrations of

very weak bases has to be mentioned. Formic acid is a much less pleasant solvent than glacial acetic acid. It is more corrosive, less stable, and it is rather difficult to remove its 2–20% water content. But the relative permittivity of anhydrous formic acid is one order of magnitude higher than those of acetic or propionic acids (see Table 2) and its acidity is also much higher. In complete agreement with these features, it is an empirical fact that extremely weak bases can be titrated in formic acid solution (especially in formic acid-acetic anhydride mixtures).

Since Ac_2O is used alone or in mixtures for nonaqueous titrations of bases not only as a reagent but also as a solvent, it is often called "acidic solvent". *USP 24* (7) lists it very diplomatically in the group of "systems for nonaqueous titrations; for titration of bases and their salts". It is an aprotic and very slightly protophilic solvent that is able to dissociate into acetyl (acid) and acetate (base) ions, and this dissociation may be characterized by a log K_{ip} constant of -14.5

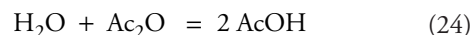


Primary and secondary amines (as well as alcohols, etc.) are acetylated by acetic anhydride in a relatively slow reaction,



and the tertiary amines can selectively be titrated in presence of amides in a mixture of glacial acetic acid and acetic anhydride (2).

In analytical chemistry, the reaction of Ac_2O with water is also important, (e.g., in the preparation of perchloric acid titrant)



Since the solutions of perchloric acid are unstable both in acetic anhydride and anhydrous formic acid, the titrant HClO_4 is used always as glacial acetic acid solution. It follows that Ac_2O and HCOOH occur in analytical chemistry practically only in mixtures and the interactions in these mixtures can be even more complicated.

The practical advantage of Ac_2O is that several very weak bases can be titrated in the presence of acetic anhydride (29), but to clarify and explain its special interactions (and those of anhydrous formic acid) needs further experimental and theoretical studies.

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