Titrations in Non-Aqueous Solvents: The Relative Strengths of Acids

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TITRATIONS IN NON–AQUEOUS SOLVENTS:
THE RELATIVE STRENGTHS OF ACIDS

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Table of Contents

I. INTRODUCTION

An understanding of the factors which are involved in acid-base process is important from both a theoretical and a practical point of view, and it would be useful to be able to predict quantitatively the course of such reactions in non-aqueous solutions. The relative order of acidity for various acids has been determined in a variety of solvents using several different techniques, and empirical relationships between these data and the corresponding information for aqueous solution exist. In this review we present an analysis of the factors involved in acid-base reactions which occur in non-aqueous solvents, in an attempt to clarify the relative importance of each. First a possible theoretical basis for establishing the intrinsic acidity of a substance based on thermochemical data is suggested. This is followed by a discussion of the factors involved when acid-base reactions occur in solution. Included in this discussion are various types of solute-solute, solvent-solvent, and solute-solvent electrostatic interactions as well as specific hydrogen-bonded interactions which can affect the course of an acid-base reaction. Finally, this analysis is applied to specific solvent systems where sufficient data are available to judge the validity of the arguments presented.

II. ACID STRENGTH

Historically, acid strengths have been described in terms of reference bases, the solvent molecule generally being the usual reference. Thus, the equilibrium constant (Equation 2) is the common thermodynamic measure of the acidity of HA for its ioni- zation in a solvent S (Equation 1). If the solvent does not interact

$$HA + S \rightleftharpoons HS^+ + A^-$$ (1)

$$K_i^{HA} = \frac{a_{HS^+} \cdot a_{A^-}}{a_{HA}}$$ (2)

with protons to an appreciable extent, for example as in the case of hydrocarbons, another reference base is used (Equation 3)

$$HA + B \rightleftharpoons HB^+ + A^-$$ (3)

In either case, the fate of the ions formed is governed by the physical properties of the solvent.

Ion association occurs in solvents with low dielectric constants, the usual measure of the extent to which this process occurs being the dissociation constant of the ion-pair formed. If the reference base is a solvent with a low dielectric constant, the dissociation process is given by Equation 4. The corresponding process occurring with a different

$$HB^+, A^- \rightleftharpoons HS^+ + A^-$$ (4)

$$K_d = \frac{a_{HS^+} \cdot a_{A^-}}{a_{HS^+,A^-}}$$ (5)

reference base in an inert solvent with a low dielectric constant is given by Equation 6.

$$HB^+, A^- \rightleftharpoons HB^+ + A^-$$ (6)

$$K_d = \frac{a_{HB^+} \cdot a_{A^-}}{a_{HB^+,A^-}}$$ (7)

For the purpose of this discussion, the intrinsic acidity of a substance can be defined by the gas phase process shown in Equation 8. Since the standard free energy change for this reaction

$$HA(g) \rightleftharpoons H^+(g) + A^-(g)$$ (8)

is related to the equilibrium constant by Equation 9, the

$$\Delta G^0 = - RT \ln K$$ (9)

intrinsic acidity can be expressed in terms of either ΔG^0 or K. It should be noted that the energy of the process in Equation 8 does *not* correspond to the H-A bond dissociation energy as it is usually defined since the latter process involves the formation of radicals. The intrinsic acidity of a substance (Equation 13) can be obtained from a thermochemical cycle involving Equations 10 to 12,

$$HA(g) \rightarrow H^{\cdot}(g) + A^{\cdot}(g) \qquad \Delta G_1^0$$ (10)

$$H^{\cdot}(g) \rightarrow H^+(g) + e^- \qquad \Delta G_2^0$$ (11)

$$A^{\cdot}(g) + e^- \rightarrow A^-(g) \qquad \Delta G_3^0$$ (12)

$$HA(g) \rightarrow H^+(g) + A^-(g) \qquad \Delta G_a^0$$ (13)
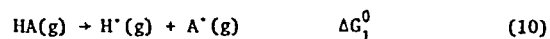
where the standard free energies correspond to the dissociation of the H-A bond (Equation 10), the ionization of hydrogen (Equation 11), and the electron affinity of the A·radical (Equation 12).

Thus, the free energy corresponding to the process in Equation 13 is given by

$$\Delta G_a^0 = \Delta G_1^0 + \Delta G_2^0 + \Delta G_3^0 \qquad (14)$$

In general the standard free energies in Equation 14, or their equivalents, are not available for calculating the intrinsic acidities of many compounds; however, estimates can be made in several series of simple compounds. Consider, as an example, the intrinsic acidities of the hydrogen halides. Recalling that the standard free energy and enthalpy are related (Equation 15) and assuming that

$$\Delta G^0 = \Delta H^0 - T \Delta S^0 \qquad (15)$$

the standard entropy terms are either negligible or so nearly the same for a group of closely related compounds that including them would not lead to a reversal of order, the standard enthalpy becomes a measure of the intrinsic acidity of a substance. Table 1 contains the pertinent enthalpy data for the hydrogen halides. The data clearly show that the intrinsic acidities of the hydrogen halides correspond to very large energies (as measured by ΔH_a^0) or very small values of the equilibrium constant for the gas phase reaction (Equation 13). In addition, the calculations show that the relative intrinsic acidity of these substances increases in the order HF <HCL<HBr<HI; this trend can be traced to a decrease in the electron affinities of the halogen atoms (ΔH_3^0) which are essentially compensated by a decrease in the bond energy of the hydrogen halides (ΔH_1^0) in the same order. The

dominant factor in the overall process is the ionization potential of hydrogen (ΔH_2^0). The order of intrinsic acidities is the same as that determined experimentally using infrared[1] and kinetic methods.[2-4] Unfortunately, data of the type shown in Table 1 are not available for more complex acids, nor is it possible to estimate the energies of these or equivalent steps by semi-empirical methods.

III. INFLUENCE OF THE SOLVENT

The relationship of the intrinsic acidity, i.e., the extent to which Equation 8 occurs, to the ionization of an acid in a basic solvent with a high dielectric constant (Equation 16) is given by the

$$HA + S \rightarrow HS^+(s) + A^-(s) \qquad (16)$$

thermochemical cycle shown in Figure 1. That is, the energy associated with the ionization of an acid in a solvent $(\Delta G_s^0$ Equation 16) is equal to that related to its intrinsic acidity (ΔG_4^0) and the ionic products $(\Delta G_5^0$ and $\Delta G_4^0)$. If the solvent has a low dielectric constant, Equation 17

TABLE 1

Standard Enthalpy Changes (Kcal/mole at 25°) Corresponding to Equations 10-13 for the Hydrogen Halides

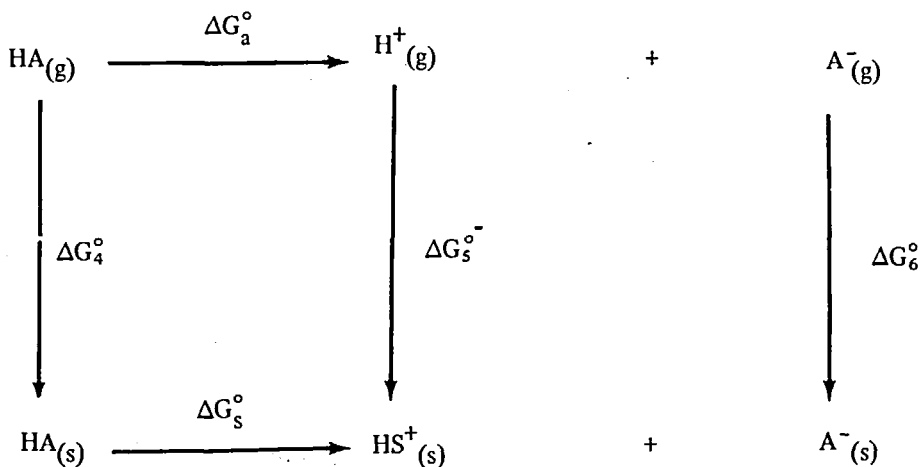| HX	Δh_1^0	ΔH_2^0	ΔH_3^0	YH⁶
HF	135.6	315.0	-83.5	367.1
HCl	103.2	315.0	-87.3	330.9
HBr	87.5	315.0	-82.0	320.5
HI	71.4	315.0	-75.7	310.7

FIGURE 1. The relationship between the intrinsic acidity of a substance and its acidity in a solvent.

$$\Delta G_s^0 = \Delta G_a - \Delta G_4^0 + \Delta G_5^0 + \Delta G_6^0 \qquad (17)$$

must be modified to include the energy corresponding to the association of the ions HS^+ and A^- into ion pairs. On the other hand, if the solvent has no basic properties, and if a reference base is used in solution, the thermochemical cycle involves first the reaction of protons with the base in the gas phase (Equation 18) followed by the solvation of the resulting ions.

$$H^+(g) + B(g) \rightarrow HB^+(g) \qquad \Delta G_{HB^+}^0 \qquad (18)$$

Under these conditions the free energy ΔG_s^0 of the acid-base reaction in solution is given by Equation 19 where ΔG_7^0 corresponds to

$$\Delta G_s^0 = \Delta G_a^0 + \Delta G_{HB^+}^0 - \Delta G_4^0 + \Delta G_6^0 + \Delta G_7^0 \qquad (19)$$

the solution of the HB^+ ion (Equation 20).

$$HB^+(g) \rightarrow HB^+(s) \qquad \Delta G_7^0 \qquad (20)$$

Unfortunately the standard free energies of solvation of many ions and molecular species in a given solvent are unknown so that the calculations corresponding to Equations 17 and/or 19 cannot be carried out. Some insight into the magnitude of the energies involved can be obtained from the standard free energies of solvation of some simple ions (Table 2). The standard free energy of solvation of H^+, which is more than two or three times that of any other monovalent ion, appears in the thermochemical cycle (Figure 1) for all acids. The standard free energy of solvation of the molecular species HA is undoubtedly markedly smaller than that for ionic species. According to Equation 17 the free energy change for the

ionization of an acid in a basic solvent with high dielectric constant is essentially a balance between the solvation energy of the ions and the free energy for the ionization of the acid in the gas phase. It should be recalled that the latter value, in the case of the hydrogen halides, is dominated by the ionization potential of hydrogen (Equation 14). Thus, the extent of ionization of an acid in a solvent depends upon how efficiently the ions are solvated by the medium. Little information is available on the free energy of solvation of molecular species in solvents other than water, and such data as are available for aqueous solutions are of little help in establishing the validity of the arguments which lead to Equations 17 and 19. The data in Table 2 do, however, provide qualitative insight into the factors which govern the extent of ionization of an acid in a solvent. The predominating factor appears to be the solvation of the proton which, together with the anion solvation energy, supplies a large fraction of the energy required to ionize the acid in the gas phase (Figure 1). It should be noted that the solvation energy of the proton is very large even in such acidic solvents as acetic acid. An additional interesting point in these data is the fact that the solvation energy of the proton in acentonitrile is less than that in acetic acid, an order which would not be expected if the relative basicity were the only factor operative.

IV. THE NATURE OF SOLVENT-SOLUTE INTERACTIONS

The extent to which a substance will solvate dissolved species is governed partially by the

TABLE 2

The Standard Free Energies of Solvation (Kcal/mole) of Some Ions in Different Solvents $(25°)^a$

Ion	NH_3	H_2O	CH_3OH	CH_3CN	CH_3CO_2H
H^+	278.0	256.5	252.5	249.0	252.0
Cl^-	68.0	74.5	73.0	64.0	70.0
Br^-	65.5	69.0	67.5	62.5	68.0
I^-	59.5	60.5	60.5	57.5	57.0
Li^+	121.0	117.0	115.0	114.5	115.0
Na^+	96.5	94.0	92.0	90.5	80.0
K^+	77.0	77.0	75.0	75.0	68.0
Rb^+	72.5	71.0	69.0	70.5	62.0
Cs^+	63.0	63.0	59.5	61.5	57.0

^{a}Ismailov, N. A., *Dokl. Akad. Nauk.*, SSSR, 149, 288, 320, 348 (1963).

intensity of the interaction between solvent molecules. Comparisons of solvent-solvent and solvent-solute interactions accordingly involve the same factors, namely, the polarity of the solvent, the magnitude of the dispersion forces, and the ability fo form hydrogen bonds. Two types of dipolar interactions have been described. The interaction between two *molecules* possessing permanent dipole moments depends upon their relative orientation. At a given temperature a statistically preferred orientation arises from the ideal orientation, i.e., the dipoles aligned parallel to a straight line, as modified by thermal effects. The potential energy of the statistical orientation is given by

$$E = \frac{-2\mu_1^2\mu_2^2}{3r^6kT} \tag{21}$$

where μ_1 and μ_2 are the magnitudes of the two dipoles at a distance r and the other symbols have their usual meanings. Thus, if the solvent molecule possesses a dipole moment, Equation 21 represents the potential energy for solvent-solvent and solute-solute interaction, as well as for the interaction of solvent molecules with the molecular form of an acid dissolved in the solvent.

The ionic products of an acid-base reaction also interact electrostatically in solution, the maximum potential energy arising from the interaction of solvent dipoles, μ, with a charged center, Ze, at a distance r being given by Equation 22.

$$E = -\frac{Ze\mu}{r^2} \tag{22}$$

For simple ionic species the corresponding solvation energy is given by

$$\Delta G = -\frac{Ne^2}{2}\left[1 - \frac{1}{D}\right]\left[\frac{1}{r_{\pm} + R_{\pm}}\right] \tag{23}$$

where D represents the bulk dielectric constant of the medium and $r_{\pm}$ is the crystallographic radius of the cation or anion. The empirical parameter $R_{\pm}$ has been chosen to fit the observed single ion free energies of solvation to the relationship shown in Equation 23 (Table 2); for simple monatomic ions R^+ has the value 0.85 and $R_{\pm}$ the value 0.25. Equation 23 is not very useful in the general case for estimating the solvation free energies of complex ionic species, such as the picrate ion, because of the ambiguity of the $(r_{\pm} + R_{\pm})$ term and the difficulties which arise from possible

localized electostatic interactions in such systems. However, the general conclusion which may be drawn from Equations 22 and 23 is that ion-dipole interactions are largest for solvents with a high dipole moment and/or a high dielectric constant. Care must be taken to recognize that solvation processes compete with solvent-solvent interactions. For example, HCN, which has a large dielectric constant(18.3 at 18°C)and a high dipole moment (2.95 Debye), is an extremely poor solvent for ionic substances. This apparently contradictory set of facts is resolved by the realization that the high dielectric constant of liquid HCN arises from strong intermolecular forces which lead to a polymeric liquid structure. In this instance the solute-solute interactions is much stonger than the interaction of the solvent with ionic species.

A second type of interaction which occurs between molcular species arises from dispersion forces, described originally by London.[6] Two nonpolar molecules which do not react chemically will attract each other by virtue of fluctuating dipoles, presumably arising from the circulation of electrons which they possess. Such dipoles induce dipoles in neighboring molecules leading to a form of dipole-dipole interaction. The magnitude of the dispersion energy is given by Equation 24

$$E = -\frac{3}{2}\frac{\alpha_1\alpha_2}{r^6}\frac{I_1I_2}{I_1 + I_2} \tag{24}$$

where α and I represent the polarizabilities and ionization potentials of the species under consideration at a distance r from each other. As in the case of the interactions previously discussed, the magnitudes of the dispersion forces operating between solvent molecules and between solvent and solute molecules must be considered in understanding the nature of the solvation process for a given system. Equation 24 indicates that dispersion forces are important at very short distances. Normally, dispersion forces are of markedly lower intensity than dipolar or Coulombic interactions; however, they are probably important in solvation processes involving hydrocarbons and their derivatives.

A third important factor in solvation processes involves specific interactions between molecular species, in contrast to the non-specific dipolar, Coulombic, or dispersion interactions discussed previously. Undoubtedly the most important of

the specific interactions involves hydrogen-bond formation. Molecules which contain hydrogen atoms covalently bound to a highly electronegative atom (usually N or O) can form hydrogen bonds to other atoms carrying unshared electron pairs (I). Hydrogen bonding is, of course, an important

$$X\text{-}H\cdots\cdots Y$$

I
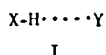
consideration for solvents which undergo auto-protolysis, since molecules in such systems can hydrogen bond to themselves as well as to solute molecules carrying unshared electron pairs. Commonly used solvents in which hydrogen bonding is important include water, ammonia, alcohols, and primary and secondary amines. The self-association of organic derivatives containing the -OH or -NRH moieties in inert solvents such as the hydrocarbons and their derivatives is usually attributed to hydrogen-bond formation between the solute molecules or between solute molecules and their conjugate base. Thus, carboxylic acids in solvents with low dielectric constants exist predominantly as hydrogen-bonded dimers (II). The

II
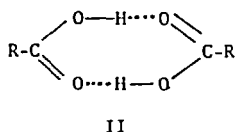
presence of excess base in a solution containing its conjugate acid gives rise to a form of hydrogen-bonded association (III) called homoconjugation; a similar association (IV) has been observed in the

$$\overset{+}{B\text{-}H}\cdots\cdots B \qquad \overset{-}{A}\cdots\cdots HA$$

III   IV

association of acids and their conjugate bases. Homoconjugation should not be confused with electrostatic association observed for ions in systems of low dielectric constants such as, for example, $NR_4^+X^-$ and $M^+\!\!\!^-$ in liquid ammonia.

V. THE RELATIVE STRENGTHS OF ACIDS

The inability to estimate quantitatively the magnitude of the factors involved in the solvation process has lead to empirical correlations of the relative acid strengths of substances in different solvents in attempt to elucidate the general way in which solvents influence acidity. The reaction of an acid HA and base B can be expressed by Equation 1 or 3. Generally the extent to which Equation 1 or 3 occurs, as measured by an equilibrium constant, is taken as a measure of the acid strength of HA. It should be noted that the magnitude of the equilibrium constant is also dependent upon the basicity of the solvent or of the references base B if the solvent is devoid of basic properties. Now if the solvent, in which the processes described by Equations 1 or 3 occur, is also the reference base, the dielectric constant of the solvent becomes important. Ion association occurs in solvents with low dielectric constants; the first process which occurs in dilute solutions involves ion-pair formation (Equation 4 or 5). Some typical values of ion-pair dissociation constants for electrolytes in several solvents are listed in Table 3. It is generally agreed that ion association becomes an important factor in solvents which have dielectric constants less than about 36.

Since the solvent can become involved in several ways in the ionization of an acid, it is well to consider intially systems where all factors are not simulataneously operative. Accordingly, we shall discuss the empirical correlations of acid-base behavior in terms of (1) the nature of the solvent, i.e., the way in which proton transfer involving the solvent occurs, (2) the inherent basicity of the solvent, and (3) the dielectric properties of the solvent.

Solvents can be conveniently classified in terms of how they are involved in the acid-base process. Inert solvents are taken to be essentially indifferent to proton transfer; that is, they can be imagined as diluents for acid-base processes. Thus, the study of acids in such solvents must involve specific reference bases (cf. Equation 3). Among the substances which act as inert solvents are saturated hydrocarbons and their chlorinated derivatives such as chloroform, carbon tetrachloride, and dichloroethane. Operationally, benzene and its derivatives have also been classified as aprotic solvents even though aromatic Π systems are now known to act as Lewis bases. It will be shown that the basic character of benzene is sufficient to affect acid-base processes. Protophilic solvents are substances which can act as proton acceptors (Equation 1) but their ability

TABLE 3

Dissociation Constants of Some Typical Electrolytes in
Several Non-Aqueous Solvents[a]

Solvent	Salt[b]	K (25°)
Ethylidine chloride	Et$_4$NPi	3.48 x 10^{-5}
(ϵ = 10.0)	Et$_4$NSCN	1.17 x 10^{-5}
	Et$_4$NClO$_4$	1.76 x 10^{-5}
	Pr$_4$NPi	3.97 x 10^{-5}
Ethylene chloride	Me$_4$NPi	0.32 x 10^{-5}
(ϵ = 10.2)	Et$_4$NPi	1.59 x 10^{-5}
	Pr$_4$NPi	1.94 x 10^{-5}
	Bu$_4$NPi	2.28 x 10^{-5}
Pyridine	NaI	0.37 x 10^{-5}
(ϵ = 12.0)	KI	0.21 x 10^{-5}
	AgNO$_3$	0.93 x 10^{-5}
	AgClO$_4$	1.91 x 10^{-5}
	Me$_4$NPi	0.67 x 10^{-5}
Acetone	KI	8.02 x 10^{-3}
(ϵ = 20.5)	KSCN	3.83 x 10^{-3}
	Me$_4$NPi	11.2 x 10^{-3}
	Et$_4$NPi	17.5 x 10^{-3}
	Bu$_4$NPi	22.3 x 10^{-3}
Nitromethane	NaPi	0.028 x 10^{-3}
(ϵ = 34.5)	KPi	0.682 x 10^{-3}
	Bu$_4$NBr	16.2 x 10^{-3}
	Me$_4$NPi	40.0 x 10^{-3}
	Et$_4$NPi	140.0 x 10^{-3}
Acetonitrile	Me$_4$NI	1.29 x 10^{-2}
(ϵ = 36.7)	Me$_4$Ni	3.62 x 10^{-2}
	Pr$_4$NI	11.0 x 10^{-2}

[a]Data taken from the tabulations in Harned, S. H., and Owen, B. B., *The Physical Chemistry of Electrolytic Solutions*, 2nd ed., Reinhold, New York, 1958.

[b]Et = ethyl; Pi = picrate, Pr = n-propyl; Me = methyl; Bu = n-butyl.

to donate protons is virtually nonexistent. Ethers, esters, ketones, and dimethylformamide are examples of protophilic solvents. Aromatic hydrocarbons and their derivatives also can be considered as weakly protophilic solvents. An amphiprotic solvent can act as either a proton donor (Equation 25) or an acceptor (Equation 26).

$$HS + B \rightarrow HB^+ + S^- \qquad (25)$$

$$HS + HA \rightarrow H_2S^+ + A^- \qquad (26)$$

Solvents such as H_2O, H_2SO_4, CH_3CO_2H, NH_3, CH_3CN, HF, and the alcohols fall into the classification.

Several methods have been used to estimate the relative basicities of solvents. The infrared method is perhaps the one for which the most extensive data are available. In this method, the X-H stretching frequency of a potentially acidic reference substance dissolved in a series of solvents is determined. The magnitude of the shift in ν(N-H), using the frequency of the substance in the gas phase where intermolecular association is at a minimum as a reference, is taken as a measure of the basicity of the solvent. The X-H stretching frequency in substances such as pyrrole and aniline [ν(N-H)] , phenol [ν(O-H)] methanol-d$_1$ [ν(O-D)] , decarborane [ν(B-H)] and HBr have been used in such an analysis for an extensive series of solvents; some of these data appear in Table 4. It is apparent that the largest infrared shifts occur in solvents to which we intuitively attribute the highest basicities. Using different reference acids a remarkably consistent order of solvent basicities is observed (Table 4). Additional correlations of this type using infrared, [1,7] ultraviolet, [8] and thermodynamic data [9,10] support the general trends observed in Table 4.

Several general observations can be drawn from the data in Table 4. Except for the saturated hydrocarbons, all solvents exhibit some degree of basicity. Indeed, such diverse solvents as inert or aprotic mesitylene, amphiprotic acetonitrile, and protophilic ethyl acetate all show much the same basicity using infrared data. If there is a general trend in the data, it appears that protophilic solvents are more basic than aprotic solvents but less basic than amphiprotic solvents, although there are exceptions such as acetonitrile. Finally, inspection of Table 4 shows that the basicity of a solvent has no obvious relationship to its dielectric constant.

A. Inert Solvents

Even though inert solvents exhibit some inherent basicity, they generally are the least basic of the solvents available. Such solvents have been used to study acid-base relationships in an attempt to establish the order of intrinsic acidities of a series of compounds. Because the solvent has virtually no basic properties of its own, such studies have been conducted with reference bases (Equation 3). If a nonbasic solvent has a dielectric

TABLE 4

The Relative Basicities and Other Properties of Common Solvents

$$\frac{\Delta \nu}{\nu} \times 10^3 \ ^c$$

Solvent	ϵ	μ debye[a]	Class[b]	νN-H[d]	νN-H[e]	νB-H[d]	νO-H[e]	ν-O-D[f]	νCl-H[g]
n-Hexane	1.9	0	i	6.8	5.2	—	8.7	—	—
Carbon tetrachloride	2.2	0	i	8.5	6.6	2.3	11.7	11.4	19.1
Chloroform	12.5	1.00	p	12.5	11.6	—	16.3	—	25.3
Carbon disulfide	2.6	0	p	13.9	13.0	2.3	—	—	—
Chlorobenzene	5.6	1.75	p	14.7	—	—	19.3	19.1 .	37.1
s-Tetrachloroethane	8.2	1.29	p	15.6	—	—	—	—	28.8
Bromobenzene	5.4	1.70	p	16.4	—	—	—	18.7	40.6
s-Tetrabromoethane	7.0	1.30	p	17.6	—	—	—	—	38.1
1,2-Dichloroethane	10.2	2.94	p	18.4	—	—	—	—	39.2
Nitromethane	35.9	3.46	am	19.8	—	—	—	—	47.1
Benzene	2.3	0	p	20.4	10.1	2.3	25.9	20.2	47.1
Nitrobenzene	34.8	4.28	p	22.9	9.0	3.8	—	24.6	68.0
Toluene	2.4	0.37	p	23.2	—	—.	—	21.0	49.2
0-Xylene	2.5	0.62	p	23.2	—	—	—	22.4	56.4
m-Xylene	2.4	0.30	p	22.9	—	—	—	22.1	56.4
p-Xylene	2.3	0	p	23.2	—	—	—	22.1	55.1
Mesitylene	2.3	0	p	25.8	9.2	3.8	—	23.9	60.3
Acetonitrile	37.5	3.96	am	30.6	11.8	—	47.9	37.5	123
Ethyl acetate	6.0	1.78	p	34.6	11.4	—	52.5	30.5	130
Butyl acetate	5.0	1.82	p	34.6	—	—	—	—	130
Acetophenone	17.4	3.03	p	35.4	—	—	—	42.6	—
Acetone	20.7	2.86	p	39.6	13.0	5.8	54.7	40.4	175
Cyclohexanone	18.3	3.08	p	47.3	—	—	—	47.8	—
Dioxane	2.2	0	p	50.2	14.7	5.8	92.3	52.2	224
Diethyl ether	4.3	1.29	p	50.4	13.0	6.2	84.4	46.7	182
Di-n-butyl ether	3.1	1.18	p	52.7	—	—	—	48.5	182
Di-isopropyl ether	3.9	1.13	p	52.7	—	—.	—	59.6	—
Pyridine	12.3	2.15	p	88.4	—	—	—	89.7	—
Triethylamine	2.4	0.61	p	97.2	—	18.5	—	117.7	—

[a]Values taken from McClellan, *Tables of Experimental Dipole Moments*, W. H. Freeman, San Francisco, 1963.

[b]i = inert; p = protophilic; am = amphiprotic.

[c]$\Delta\nu$ is the difference in frequency between the vapor state, ν, and that found in solution for the stretching modes indicated.

[d]νNH for pyrrole. Bellamy, L. J., Hallam, E. H., and Williams, R. L., *Trans. Faraday Soc.*, 54, 1120 (1958).

[e]νNH for aniline, B-H for decaborane, $B_{10}H_{14}$, νOH for phenol. Bellamy, L. J., Hallam, E. H., and Wiiams, R. L., *Trans. Faraday Soc.*, 54, 1120 (1958).

[f]νO-D for CH_3OD. Gordy, W., *J. Chem. Phys.*, 9, 215 (1941).

[g]νCl-H for HCl. Josien, M. L. and Sourisseau, G., *Bull. Soc. Chim. France*, 1955, 178.

constant above about 36, little ion association occurs; however, this combination of properties is highly unusual among solvents (Table 4). Solvents with low basicity generally have low dielectric constants so that ion association becomes an important process (Equation 27). By using an aprotic

$$BH^+ + A^- \rightleftarrows BH^+, A^- \qquad (27)$$

solvent with a sufficiently low dielectric constant, such as benzene ($\epsilon = 2.3$), the dissociation process (Equation 27) becomes negligible so that acid-base reactions are best represented by Equation 28. The acidity of substances relative to a given

$$B + HA \rightleftarrows BH^+, A^- \qquad (28)$$

base under such conditions is measured by an equilibrium constant of the usual form (Equation 29). The extent to which reaction

$$K_a = \frac{[BH^+, A^-]}{[B][HA]} \qquad (29)$$

29 occurs under these conditions has been measured using quantitative spectroscopic techniques.

Usually the reference base is an indicator which exhibits different spectra in its neutral (B) and protonated (BH⁺) forms. Operationally, known quantities of the indicator base and acid are mixed and the concentration of the unreacted base and/or the protonated base is determined spectophotometrically. Using standard mathematical techniques[11] the value of the equilibrium constant (Equation 29) can be determined. Similar methods can be used to measure the relative basicities of substances using a single indicator acid. The results of such experiments are reported in a subsequent section.

In addition to the indicator method, potentiometric methods have been devised to estimate the extent to which an acid ionizes. The potentiometric method finds most use in solvents in the intermediate-to-high dielectric constant range, although an attempt at using this method in benzene has been reported.[18] There are reports of using electrodes incorporating nonaqueous solvents, e.g., the chloranil electrode in acetic acid[12] and the quinhydrone electrode in formic acid,[13] but an electrode incorporting nonaqueous/aqueous liquid junctions, such as the glass electrode,[14] has been more often employed. In some instances attempts have been made to calibrate such electrodes using buffer systems prepared in the solvent in question,[15,16] but most often the half-neutralization potential has been used as a measure of the relative acidity of a series of acids. Indeed, a relative acidity scale for a number of nonaqueous solvents has recently been suggested on the basis of the order of the half-neutralization potentials for the neutralization of $HClO_4$ with $(C_2H_5)_4NOH$ in these solvents.[17]

The apparent advantage obtained by studying acid-base behavior in inert solvents of low dielectric constant and low basicity is lost, to some extent, by intermolecular association phenomena which give rise to other equilibria that sometimes confuse the interpretation of the results. In other words, the decrease in the intensity of the interactions involving solvent molecules makes possible solute-solute interactions more important. Although ionic solvation is suppressed in these solvents (cf. Equations 22 and 23) nonspecific solvent-solvent and solute-solute interactions arising from dispersion forces become important. In many instances, however, the effects of hydrogen bonding dominate the nature of the equilibria in such solutions. Hydrogen bonding among the

molecules of typical inert solvents is usually unimportant, but solute-solute interactions among the reactants and/or products of acid-base reaction (Equations 27 and 28) involving hydrogen bonds are common. Thus, a consideration of self-association of acids, bases, and salts serves as a convenient focus for a discussion of hydrogen-bonded interactions in acid-base reactions occuring in inert solvents.

The majority of the acidic species for which hydrogen-bonded associations have been observed contain the -OH moiety.[19] It is well known that alcohols are associated in inert solvents, with the more acidic phenols forming markedly more stable aggregates. A variety of physical methods has been used to study the self-association of phenols in aprotic solvents, including distribution,[20] spectroscopic (infrared,[21] untraviolet,[22] nuclear magnetic resonance[23]), and vapor pressure studies.[24] The results, in general, have been interpreted in terms of the formation of dimers or higher polymeric species. Infrared studies[25] have shown that a single alkyl group in an ortho position (v) does not affect the ability to form hydrogen bonds, but substituents in both the 2 and 6 positions (VI) — especially if they are bulky — markedly decrease the degree of association. Phenols carrying substituents such as -NO_2 in the 2 and/or 6 position (VII) which can form intra-

V VI VII
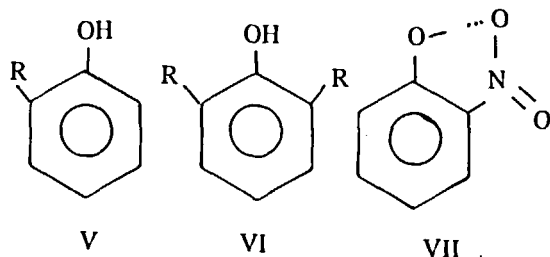
molecular hydrogen bonds are monomeric[26] in contrast with isomers carrying the same substituents at the other ring positions. It is necessary to recognize the tendency of phenols to associate because many indicators that are useful in inert solvents are phenolic in nature. For example, the degree of association of an indicator might become an important consideration if it is to be used in quantitative spectral studies.[27] It should also be recognized that 2,4-dinitrophenol has been used as a reference acid in such solvent systems to establish relative basicity scales with little con-

sideration for possible differences among the structures of the products formed in different solvents.

The tendency of carboxylic acids to associate in the vapor phase is also observed in inert solvents. Although higher polymers have been postulated,[28] the monomer-dimer equilibrium is generally considered the most important in these systems. Both aliphatic an aromatic carboxylic acids have been extensively studied. In both cases the dimer has been formulated as a hydrogen-bonded species (II and VIII). However, *ortho*-substituted benzoic acids can be either dimeric (VIII) or monomeric (IX) depending upon the ability of the substituent to form hydrogen bonds.

VIII

X = OR, NH₂
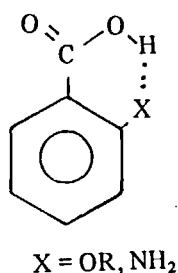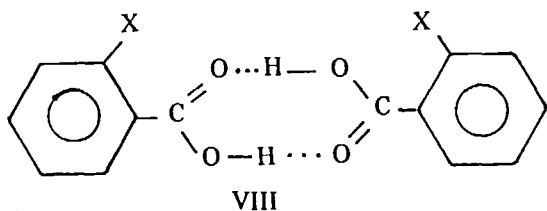
IX

Dimerization constants (Equation 30) have been determined using

$$2 \ RCO_2H \ \rightleftarrows \ (RCO_2H)_2 \tag{30}$$

a variety of physical methods including nmr,[29] electronic[30-33] and infrared spectroscopy,[34-38] acoustical absorption,[39,40] distribution,[41,42] heats of dilution,[43,44] dielectric polarization,[45-49] isopiestic methods,[52] and studies of colligative properties.[51-53] The dimerization constants for several carboxylic acids in benzene solution appear in Table 5. It is apparent from these data that in general the tendency to dimerize decreases with increasing acidity of the acid, as measured by its aqueous pK_a value. Acids for

| Acid	$\log K_d$ [a]	pK_a (H_2O)	Reference
o-CH₃O-C₆H₄-CO₂H	0.59	4.09	b
Cl₃C-CO₂H	0.13	0.64	c
o-NO₂-C₆H₄-CO₂H	1.92	2.17	b
o-Br-C₆H₄-CO₂H	2.41	2.85	b
o-I-C₆H₄-CO₂H	2.44	2.86	b
o-Cl-C₆H₄-CO₂H	2.41	2.94	b
o-F-C₆H₄-CO₂H	2.48	3.27	b
o-CH₃-C₆H₄-CO₂H	2.63	3.91	d
C₆H₅CO₂H	2.79	4.20	d

[a]Expressed for the process monomer ⇌ dimer.

[b]LeFèvre, R. J. W. and Vine, H., *J. Chem. Soc.*, 1795 (1938).

[c]Dunken, H. and Jäger, G., *Z. Chem.*, 3, 432 (1963).

[d]Wall, F. T. and Banes, F. W., *J. Amer. Chem. Soc.*, 67, 898 (1945).

which intramolecular hydrogen bonding is possible (IX), e.g., certain *ortho*-substituted benzoic acids such as *o*-methoxybenzoic acid, have assiciation constants that are markedly lower than those for the acids listed in Table 5. The small, but measurable, differences among the basicities of these aprotic solvents affect the extent of dimerization of benzoic acids. Thus, the degree of dimerization of benzoic acids in aprotic solvents decreases in the order[54]

$$\underline{n}\text{-hexane} < CCl_4 < CS_2 < CHCl_3$$
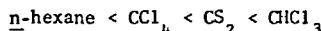
which is also in the order of increasing basicity of these substances (Table 4). A study of the free energies of the dimerization reactions for benzoic acid in several solvents (Table 6) shows that a direct relationship exists between these quantities and the infrared measure of basicity of these solvents shown in Table 4. In other words, the solute-solvent hydrogen-bonding interactions become more important in competing with the corresponding solute-solute interactions. Similar behavior occurs for the dimerization of acetic acid in various solvents (Table 7). That is, the dimer is the most stable in solvents with very low basicities, such as cyclohexane and heptane, but the dimers are less stable in the more basic solvents benzene and 1,1-dichloroethane. In the markedly more basic protophilic solvents acetonitrile[54] and dimethyl sulfoxide[37] the dimerization of benzoic acid is not

TABLE 6

The Free Energy of Dimerization of Benzoic Acid in Several Solvents (25°)[a]

Solvent	$-\Delta G$, Kcal/mole
Cyclohexane	6.07
Carbon tetrachloride	5.69
Chlorobenzene	4.45
Toluene	4.00
Benzene	3.82
Chloroform	3.60

[a]Maier, W., *J. Chim. Phys.*, 61, 239 (1964).

TABLE 7

Dimerization Constants of Acetic Acid in Several Solvents Near 25°C

Solvent	K	Reference
Heptane	2.22×10^{-4}	a
Cyclohexane	1.85×10^{-4}	b
Carbon Tetrachloride	4×10^{-3}	c
Benzene	5×10^{-2}	d
1,1-Dichloroethane	16.4	b

[a]Pohl, H. A., Hobbs, M. E., and Gross, P. M., *J. Chem. Phys.*, 9, 408 (1941).

[b]Reeves, L. W. and Schneider, W. G., *Trans. Faraday Soc.*, 54, 314 (1958).

[c]Harris, J. T. and Hobbs, M. E., *J. Amer. Chem. Soc.*, 76, 1419 (1954).

[d]Satchell, D. P. N. and Wordell, J. L., *Trans. Faraday Soc.*, 61, 1199 (1965).

measurable, rather strong hydrogen-bonded solvent-solute interaction having been detected using spectroscopic methods. The dimerization process for carboxylic acids is also affected by traces of water in the aprotic solvents. Indeed, trichloroacetic acid in benzene apparently forms a hydrate of composition $CCl_3CO_2H \cdot H_2O$ in preference to the dimer.[52] Such results suggest that dimerization constants determined by the distribution method do not truly reflect the extent to which equilibrium 18 occurs.[55] It is conceivable that the results of experiments with inert solvents in which care is not taken to exclude moisture can lead to erroneous interpretation of the acidities of the substances in question. Substances which are intrinsically more acidic than carboxylic acids also associate in aprotic solvents. Thus, nitric acid,[56-58] phosphorous-containing acids,[59-65] and sulfur-containing acids[66-68] undergo hydrogen-bonded associations.

Primary and secondary amines are known to associate through hydrogen bond formation in inert solvents, in contrast to the tertiary amines. Evidence for association comes from studies of the heats of mixing of amines with weak proton donors,[69] from Raman and infrared spectroscopy[70-75] and nmr spectroscopy,[76-78] and from vapor pressure measurements.[79] Results have been interpreted in terms of equilibria between monomers, dimers, and higher polymers.

The association of the ionic species formed in acid-base reactions occuring in inert solvents forms the basis for the last part of the discussion in this section. Since most reference bases used in inert solvents are derivatives of ammonia, the salts formed (Equation 28) contain at least one N-H bond. Extensive information is available from a variety of techniques which indicates that the ion pairs BH^+, A^- formed in inert solvents are hydrogen-bonded and should more properly be described as $BH^+, \cdots A^-$ rather than the electrostatic ion pair. For example, the results of conductivity experiments conducted on quaternary ammonium salts and incompletely substituted ammonium salts indicate that the former exhibit significantly higher dissociation constants than the latter in inert solvents under the same conditions. Table 8 contains selected data illustrating this point. Hydrogen bonding in quaternary ammonium salts is impossible, so that the ion pairs in such systems are bound by purely electrostatic forces. The decrease in the dissociation constants of ion pairs containing partially substituted ammonium ions has been attributed to a stronger interaction than expected for simple electrostatic interactions; such results have been interpreted in terms of hydrogen bonding.[80] The nature of the anion in hydrogen-bonded ion pairs also affects the magnitude of the dissociation constant (Table 9), an effect which obviously reflects its relative basicity. The interactions of aliphatic carboxylic acids[81-83] and benzoic acid[84] with primary, secondary, and tertiary amines in benzene have been studied using dielectric measurements. Secondary ammonium carboxylate ions are best formulated in terms of two hydrogen bonds (X). Benzoic acid, in its
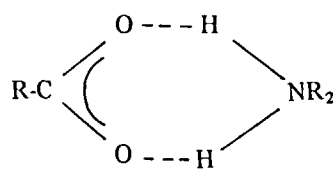
X

TABLE 8

Ion-pair Dissociation Constants (Log K_i) of Some Ammonium
Salts in Several Solvents (25°)

Ammonium salt[a]

Solvent	ϵ	Cation	log K	Cation	log K	Reference
C_6H_6	2.3	i-Am_4N^+	-17.05	i-Am_3NH^+	-20.60	b
C_6H_5Cl	5.6	Bu_4N^+	- 7.3	Bu_3NH^+	-12.68	c
$ClCH_2CH_2Cl$	10.2	Bu_4N^+	- 3.64	Bu_3NH^+	- 7.68	d
C_5H_5N	12.3	Bu_4N^+	- 2.91	NH_4^+	- 3.55	e
CH_3COCH_3	20.7	Bu_4N^+	- 1.65	NH_4^+	- 2.95	f
$C_6H_5NO_2$	34.8	Bu_4N^+	- 0.7	Bu_3NH^+	- 3.72	g

[a]i-Am = isoamyl; Bu = n-butyl.
[b]Fuoss, R. M. and Kraus, C. A., *J. Amer. Chem. Soc.*, 55, 3614 (1933).
[c]McIntosh, R. L., Mead, D. J., and Fuoss, R. M., *J. Amer. Chem. Soc.*, 62, 506 (1940).
[d]Mead, D. J., Kraus, C. A., and Fuoss, R. M., *J. Amer. Chem. Soc.*, 61, 3257 (1939).
[e]Burgess, D. S. and Kraus, C. A., *J. Amer. Chem. Soc.*, 70, 706 (1948).
[f]McDowell, M. J. and Kraus, C. A., *J. Amer. Chem. Soc.*, 73, 3293 (1951).
[g]Witschonke, C. R. and Kraus, C. A., *J. Amer. Chem. Soc.*, 69, 2471 (1947).

TABLE 9

Cation Homoconjugation Constants Near 25°C

| Solvent	ϵ	Cation	Anion	log K	Reference
$ClCH_2CH_2Cl$	10.2	PyH^+	ClO_4^-	-6.3	a
		PyH^+	Pi^-	-7.4	a
$C_6H_5NO_2$	34.8	$BuNH_3^+$	ClO_4^-	-2.60	b
		$BuNH_3^+$	Pi^-	-3.83	b
		Bu_3NH^+	Pi^-	-3.72	b
		Bu_3NH^+	I^-	-4.02	b

[a]Fuoss, R. M. and Kraus, C. A., *J. Amer. Chem. Soc.*, 55, 3614 (1933).

[b]Witschonke, C. R. and Kraus, C. A., *J. Amer. Chem. Soc.*, 69, 2471 (1947).

dimeric form, reacts with amines to form species of the types $B(HA)_2$, BHA, and $(BHA)_2$. The dipole moments of these species suggest that extensive hydrogen bonding is present in these systems. The first intermediate, $B(HA)_2$, has been formulated as a partially neutralized benzoic acid dimer XI, primary or secondary amines forming an internally hydrogen-bonded system (XIa) which is not possible with tertiary amines (XIb). Salts with the expected stoichiometry, BHA, are formed only by tertiary amines, in contrast to the primary and secondary amines which give the dimeric salts $(BHA)_2$. The


IX
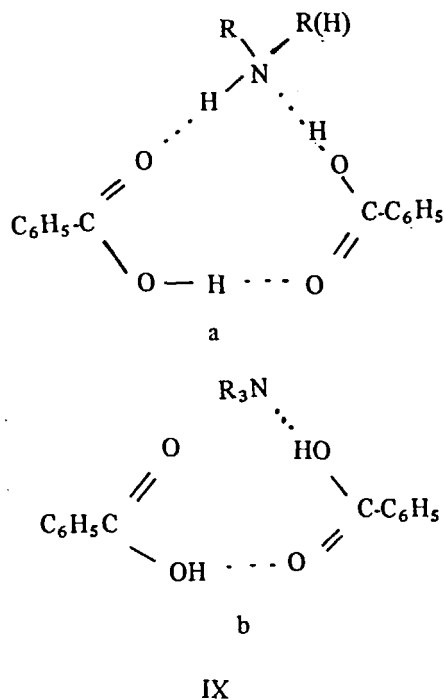
latter also have been formulated as hydrogen-bonded ion pairs (XII). These general conclusions are supported by vapor-pressure measurements[85] and infrared data.[86-88] There have been suggestions, based on detailed analysis of infrared data, that when such reactions occur in chloroform the solvent can stabilize the intermediate salt by
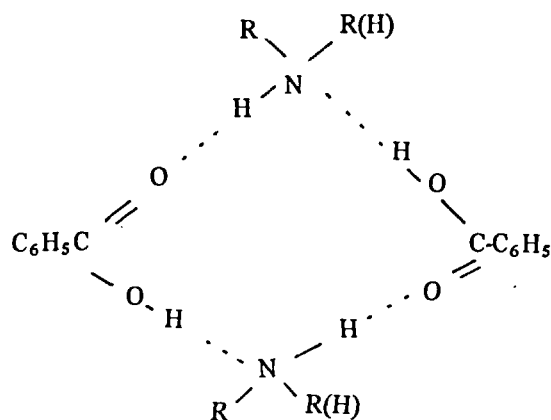
XII

hydrogen bonding from a solvent molecule, e.g., XIII. It has also been claimed, from infrared evidence, that the reaction of pyridine with carboxylic acids in chloroform or acentontrile gives two extreme types of salts.[89,90] With relatively weak acids such as CH_3CO_2H [$pK_a(H_2O)$ = 4.8] and $ClCH_2CH_2CO_2H$ [$pK_a(H_2O)$ = 4.1] the product is best described as a complex in which the acid is hydrogen bonded to the base
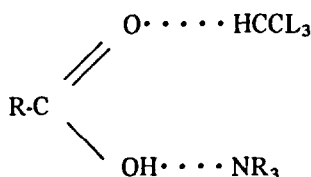
XIII

XIV that is, proton transfer has not occurred. At the other extreme, the strongest acids such as CX_3CO_2H [X=F, $pK_a(H_2O)$ = 0.23; X=Cl, $pK_a(H_2O)$ = 0.70] are supposed to consist of hydrogen-bonded ion pairs in which the proton has been transferred to the base (XV). The salts formed from acids of an intermediate strength, such as RCO_2H [R= CH_2I, $pK_a(H_2O)$ = 3.12; R=

$$Py \cdots HA \qquad\qquad PyH^+ \cdots\cdots A^-$$

XIV   XV

CH_2CH_2Cl,(H_2O) = 2.81], consist of a tautomeric mixture of products (XVI $\rightleftarrows$ XV). Infrared spectroscopic studies using acids and bases with varying strengths show that a change in the
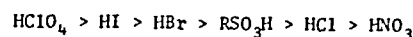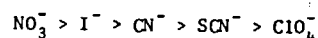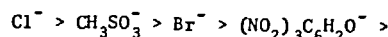
spectroscopic characteristics which signals a change from XIV to XV occurs near a $\Delta pK_a(H_2O)$ value (Equation 31) of 3.75. As might be expected, results obtained with phenols using different bases behave in a similar way.[91] The difference in the two hydrogen-bonded species XIV and XV has been detected for phenols using ultraviolet-visible spectroscopy.[91]

$$\Delta pK_a(H_2O) = pK_a(base) - pK_a(acid) \qquad (31)$$

The ability of anions to hydrogen bond to a reference acid has been determined by measuring the chemical shift of the N-H proton in the trioctylammonium salts $R_3NH^+ \cdots X^-$ dissolved in benzene.[92] The relative hydrogen-bonding ability of some common anions decrease in the order which is in approximately the reverse order of the strengths of the corresponding acids determined from indicator or kinetic studies.[2-4] It is apparent that the ability of anions to accept protons depends upon a complex combination of factors including charge, size, polarizability, and steric effects.[93,94]

$$Cl^- > CH_3SO_3^- > Br^- > (NO_2)_3C_6H_2O^- >$$
$$NO_3^- > I^- > CN^- > SCN^- > ClO_4^-$$

$$HClO_4 > HI > HBr > RSO_3H > HCl > HNO_3$$

Hydrogen-bonding effects in salts of the type BHA can become an important consideration if one of the components is an acid or base indicator that is used to establish relative acidity scales or the endpoint of a titration in an inert solvent. For example, bromophthalein magenta undergoes a complex and continuous color change in the presence of different bases at different concentrations, which has been interpreted in terms of hydrogen bonding.[95-98] Similar behavior is observed for bromophenol blue.[99] bromocresol green,[99] picric acid,[100] and trinitro-m-cresol.[100] Thus, techniques involving visual or spectroscopic detection methods must be carefully designed.

The products of an acid-base reaction which we have written as the ion pair BH^+A^- can be hydrogen bonded to neutral molecules rather than to each other. Thus, in a protic solvent of low basicity the cation BH^+ could be associated with another molecule of base (XVI), whereas the anion might be associated with the acid (XVII). The ions formed by such associations have been designated

$$BH^+ \cdots B \qquad\qquad A^- \cdots HA$$

$$XVI \qquad\qquad\qquad XVII$$

as conjugate ions.[101] Homoconjugate ions contain the same acid ($A^- \cdots HA$) or base ($BH^+ \cdots B'$ constituents, whereas heteroconjugate ions incorporate different constituents ($BH^+ \cdots B$ and $A' \cdots HA'$). The formation of homo- and heteroconjugate cations has been detected in inert solvents using spectroscopic[95,97] and conductance methods.[102,103] Relatively little information is available concerning the magnitude of the equilibrium constant for the formation of conjugate cations in aprotic solvents (Equation 32 or 33) because of the difficulty of

$$BH^+ + B \rightleftarrows BH^+ \cdots B \qquad\qquad (32)$$

$$BH^+ \cdots A + B \rightleftarrows BH^+ \cdots B + A^- \qquad (33)$$
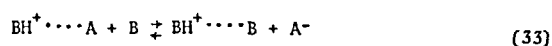
unambiguously interpreting the data from solutions containing complex equilibria. However, formation constants in the range of $\ll 1$, for Equation 33,[102] to 10^7 for Equation 26,[103] have been reported. Experimental evidence is also available for the existence of homo- and heteroconjugate anions in inert solvents from spectroscopic,[104-108] conductometric,[109-111] cryoscopic,[112] and potentiometric measurements. Although conjugate anions have been more widely studied than conjugate cations, there is little information concerning the magnitude of their formation constants. As might be expected, conjugate anions are prevalent for carboxylate and phenolate ions, but homoconjugate anions of strong mineral acids have also been detected. For example, conductivity studies in benzene have been interpreted[110] to show the existence of $ClHCl^-$ and $ClHNO_3^-$. The shift in νH-A when H-A is dissolved in inert solvents containing quaternary ammonium halides has been attributed to the formation of the heteroconjugate halide anions $X^- \cdots H\text{-}A$ (HA = HCl,[114] HNO_3.[110] H_2O,[115] ROH[116-118]). The data available seem to support the suggestion that homoconjugate anion formation is encouraged in solvents with low proton donating ability; there appears to be little correlation with the dielectric constant of the solvent. Under these conditions the acid H-A stabilized the anion A^- by "solvation" in much the same way as does a solvent, such as water, with a higher proton-donating ability. Conversely, in solvents with a low basicity,

cations can be stabilized by excess base giving rise to conjugate cations. In a sense the process of homoconjugation can be imagined as being analogous to the autoprotolytic reactions which occur in amphiprotic solvents. In the case of conjugate ion formation, the reaction occurs because the medium is virtually inert. The formation of conjugate ions predominates when excess acid or base is present in solutions containing the salt BH^+A^- a situation which occurs near the endpoint of a titration. Thus, the formation of conjugate ions must be considered in interpreting titration data obtained in inert solvents using conductometric,[119,120] potentiometric,[113] and spectroscopic methods.[104,107]

The practical aspects associated with conjugate ion formation are many. For example, visual endpoints in titration of alkaloids with p-toluenesulfonic acids in CCl_4 are sharper in the presence of 1% C_6H_5OH, which probably enhances the strength of the titrant as a result of hydrogen-bond formation from the phenol[121,122] Similarly, the strength of HCl in dioxane is increased by the addition of any of a series of alcohols which serve as hydrogen-bond donors. Finally, since water, a common potential contaminant, can act as the acid in the formation of homoconjugate anions, considerable care must be taken in interpreting results obtained in solvents which may be wet.

Although potentiometric methods have been employed in aprotic solvents,[18,123] the scales of relative acidities available have been developed by estimating the value of the equilibrium constant (Equation 29) from spectrophotometric measurements. The method must be applied with care because of the subtle interactions that can occur between the species in solution (vide supra) that can affect the spectral results. Extensive tabulations of relative acidities and basicities in aprotic solvents are available.[124] However, we are not concerned with the relationships that have been deduced between acidity or basicity, and molecular structure. Rather, the object at hand is whether the results of acid-base studies in nonaqueous solvents relflect absolute acidities as has been often suggested. Conceptually, the energy cycle shown in Figure 1 suggests that such might be the case because solvation effects on the components of acid-base reactions are of low intensity and, hopefully, might either cancel or be of negligible importance.

Unfortunately, consistent data in a variety of inert solvents are not available for extensive comparison. However, the results for a sufficient number of pairs of acids or bases can be obtained from the literature to yield some tentative conclusions. If the equilibrium constant, K_{BHA}, for Equation 28 reflects only the relative acidity of HA, then the relative acidities of two acids referred to the same bases in two different solvents should be the same. Similar observations should obtain for the relative basicities of two bases. A variety of examples of differences between $\Delta p K_{BHA}$ values in different solvents appears in Tables 10 and 11. Also listed in these tables are the reference acids or bases, the dielectric constants of the solvents, and the relative basicity of the solvent as expressed in the order

n-heptane (1) $<$ CCl_4 (2) $<$ $CHCl_3$ (3) $<$ C_6H_5Cl (4) $<$ C_6H_5Br (5) $<$ CH_2Cl_2 (6) $<$ C_6H_6 (7) $<$ $C_6H_5CH_3$ (8)

TABLE 10

$\Delta p K_{BHA}$ for Several Acid Pairs in Different Solvents

HA_1[a]	pK_{BHA_1}	HA_2[a]	pK_{BHA_2}	Base	$\Delta p K_{BHA}$	Solvent	Relative basicity[b]	t, °C	Ref.
PC	1.83	P	2.06	$C_4H_9NH_2$	0.23	C_7H_{16}	1	25	c
PC	1.92	P	1.99	$(C_4H_9)_2NH$	0.07	C_7H_{16}	1	25	c
PC	1.74	P	1.92	$(C_2H_5)_3N$	0.18	C_7H_{16}	1	25	c
PC	1.53	P	1.55	C_5H_5N	0.02	CCl_4	2	27	d
PC	0.44	P	0.60	$C_6H_5NH_2$	0.16	CCl_4	2	27	d
P	2.06	1-N	2.16	$C_4H_9NH_2$	0.10	C_7H_{16}	1	25	c
P	2.11	1-N	2.21	$(C_4H_9)_2NH$	0.10	C_7H_{16}	1	25	c
P	1.92	1-N	2.08	$(C_2H_5)_3N$	0.16	C_7H_{16}	1	25	c
P	1.78	1-N	1.92	C_5H_5N	0.14	CCl_4	2	20	e, f
P	1.96	1-N	2.04	$(C_2H_5)_3N$	0.08	CCl_4	2	20	f
P	1.35	1-N	1.49	$(C_3H_7)_3N$	0.14	CCl_4	2	20	f
P	1.47	1-N	1.65	$(C_4H_9)_3N$	0.18	CCl_4	2	20	f
P	0.43	1-N	0.28	$(C_6H_3CH_3)_3N$	0.15	CCl_4	2	20	f
P	3.57	1-N	3.80	$(CH_3)_3NO$	0.23	CH_2Cl_2	6	20.7	g
2,4-DPN	-0.1	P	1.26	C_5H_5N	1.36	C_6H_6	7	25	h
2,4-DPN	2.56	P	2.11	$(C_4H_9)_2NH$	-0.45	C_7H_{16}	1	25	c, l
2,4-DPN	-0.1	4-NP	2.04	C_5H_5N	2.14	C_6H_6	7	25	h
2,4-DPN	3.50	4-NP	2.42	$(C_2H_5)_3N$	-1.08	C_6H_6	7	25	i
2,4-DPN	1.97	4-NP	2.18	$(C_3H_7)_3N$	0.21	C_6H_6	7	25	i
2,4-DPN	3.23	4-NP	2.76	$(C_2H_5)_2NH$	0.47	C_6H_6	7	25	i
P	1.62	HPi	3.73	C_5H_5N	2.11	CCl_4	2	25	j, k
P	1.26	HPi	3.62	C_5H_5N	2.36	C_6H_6	7	25	h, k

[a] PC = p-cresol; P = phenol; 1-N = 1-naphthol; 2,4-DNP = 2,4-$(NO_2)_2$-C_6H_3-OH; 4-NP = 4-NO_2-C_6H_4-OH; HPi = picric acid

[b] As determined from Table 4.

[c] Bonnet, M. and Julg, A., *J. Chim. Phys.*, 59, 723 (1962).

[d] Dierckx, A.-M., Huyskens, P., and Zeegers-Huyskens, T., *J. Chim. Phys.*, 62, 336 (1965).

[e] Dunken, H. and Fritzsche, H., *Z. Chem.*, 1, 249 (1961).

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[i] Anderson, A. R., Dissertation, Ph.D., University of Newcastle, 1954.

[j] Biggs, A. I. and Robinson, R. A., *J. Chem. Soc.*, 388 (1961).

[k] Jasiński, T., Misiak, T., and Skarzyńska, T., *Roczniki Chem.*, 39, 1549 (1965).

[l] Pearson, R. G. and Vogelsong, D. C., *J. Amer. Chem. Soc.*, 80, 1038 (1958).

TABLE 11

pK_{BHA} for Several Acid Pairs in Different Solvents

B_1	pK_{B_1HA}	$B_2{}^a$	pK_{B_2HA}	Acid[a]	pK_{BHA}	Solvent	Relative basicity[b]	t, °C	Ref.
$(C_4H_9)_3N$	3.96	$(C_2H_5)_3N$	4.20	2,4-DNP	0.24	$CHCl_3$	3	25	c
$(C_4H_9)_3N$	2.82	$(C_2H_5)_3N$	3.47	2,4-DNP	0.65	C_6H_6	7	25	d
$(C_4H_9)_3N$	3.58	$(C_2H_5)_3N$	3.99	2,4-DNP	0.41	C_6H_5Cl	4	25	c
$(C_4H_9)_3N$	0.61	$(C_2H_5)_3N$	0.81	CH_3OH	0.20	CCl_4	2	20	e
$(C_4H_9)_3N$	1.47	$(C_2H_5)_3N$	1.96	P	0.49	CCl_4	2	20	e
$(C_4H_9)_3N$	1.65	$(C_2H_5)_3N$	2.04	1-NP	0.78	CCl_4	2	20	e
$(C_3H_7)_3N$	2.81	$(C_2H_5)_3N$	2.46	4-NP	-0.35	C_6H_6	7	25	d
$(C_3H_7)_3N$	1.97	$(C_2H_5)_3N$	3.47	2,4-DNP	1.50	C_6H_6	7	25	d
$C_3H_7NH_2$	2.81	$(C_2H_5)_2NH$	2.76	4-NP	-0.05	C_6H_6	7	25	d
$C_3H_7NH_2$	1.97	$(C_2H_5)_2NH$	3.09	2,4-DNP	1.12	C_6H_6	7	25	d
$(C_2H_5)_2NH$	2.76	$(C_2H_5)_3N$	2.46	4-NP	-0.30	C_6H_6	7	25	d
$(C_2H_5)_2NH$	3.09	$(C_2H_5)_3N$	3.47	2,4-DNP	0.38	C_6H_6	7	25	d
$(C_2H_5)_2NH$	3.40	$(C_2H_5)_3N$	3.99	2,4-DNP	0.59	C_6H_5Cl	4	25	c
$(C_2H_5)_2NH$	3.24	$(C_2H_5)_3N$	4.20	2,4-DNP	0.96	$CHCl_3$	3	25	c
$(C_4H_9)_2NH$	3.02	$(C_2H_5)_3N$	3.50	2,4-DNP	0.48	C_6H_6	7	25	d
$(C_4H_9)_2NH$	3.41	$(C_2H_5)_3N$	4.20	2,4-DNP	0.79	$CHCl_3$	3	25	c
$(C_4H_9)_2NH$	3.40	$(C_2H_5)_3N$	3.99	2,4-DNP	0.59	C_6H_5Cl	4	25	c
$(C_4H_9)_2NH$	1.92	$(C_2H_5)_3N$	1.74	PC	-0.18	C_7H_{16}	1	25	f
$(C_4H_9)_2NH$	2.06	$(C_2H_5)_3N$	1.92	P	-0.14	C_7H_{16}	1	25	f
$(C_4H_9)_2NH$	2.11	$(C_2H_5)_3N$	2.01	2-N	-0.10	C_7H_{16}	1	25	f
C_5H_5N	0.78	C	0.88	CH_3OH	0.10	CCl_4	2	20	e
C_5H_5N	1.92	C	2.30	1-N	0.38	CCl_4	2	20	e
C_5H_5N	2.05	C	2.35	PCP	0.30	CCl_4	2	20	e
$(C_4H_9)_2NH$	3.05	$(C_4H_9)_3N$	2.82	2,4-DNP	-0.23	C_6H_6	7	25	g
$(C_4H_9)_2NH$	2.96	$(C_4H_9)_3N$	2.70	2,4-DNP	-0.26	$C_6H_5CH_3$	8	25	g
$(C_4H_9)_2NH$	3.40	$(C_4H_9)_3N$	3.58	2,4-DNP	0.18	C_6H_5Cl	4	25	g
$(C_4H_9)_2NH$	3.48	$(C_4H_9)_3N$	3.66	2,4-DNP	0.18	C_6H_5Br	5	25	g
$(C_4H_9)_2NH$	3.35	$(C_4H_9)_3N$	3.62	2,4-DNP	0.27	C_6H_5F	–	25	g
$(C_4H_9)_2NH$	3.41	$(C_4H_9)_3N$	3.96	2,4-DNP	0.55	$CHCl_3$	3	25	c
$(C_4H_9)_2NH$	2.56	$(C_4H_9)_3N$	2.00	2,4-DNP	-0.56	C_7H_{16}	1	25	c
C_5H_5N	3.40	$4\text{-}CH_3\text{-}C_5H_4N$	4.46	BPB	1.06	C_6H_5Cl	4	25	c
C_5H_5N	1.62	$4\text{-}CH_3\text{-}C_5H_4N$	1.92	P	0.30	CCl_4	2	25	h

[a] C = collidine; 2,4-DNP = $2,4\text{-}(NO_2)_2\text{-}C_6H_3\text{-}OH$; 4-NP = $4\text{-}NO_2\text{-}C_6H_4\text{-}OH$; PC = p-cresol; 1-N-naphthol; 2-N = 2-naphthol; PCP = C_6Cl_5OH; PPB = bromphenol blue; P = C_6H_5OH.

[b] Determined from Table 4.

[c] Pearson, R. G. and Vogelsong, D. C., *J. Amer. Chem. Soc.*, 80, 1038 (1958).

[d] Anderson, A. R., Ph.D. Dissertation, University of Newcastle, 1954.

[e] Gramstad, T., *Acta Chem. Scand.*, 16, 807 (1962).

[f] Bonnet, M. and Julg, A., *J. Chim. Phys.*, 59, 723 (1962).

[g] Bayles, J. W. and Taylor, A. F., *J. Chem. Soc.*, 417 (1961).

[h] Halleux, A., *Bull. Soc. Chim. Belg.*, 68, 318 (1959).

The order was taken from the infrared data in Table 4. Inspection of the data in Table 10 shows that the differences in acid strengths are reasonably constant for solvents of low basicity (n-heptane and CCl₄), but marked discrepancies occur in the more basic solvents benzene and CH₂Cl₂. Indeed, in some instances the order of acidities is reversed in going from less basic solvents to more basic ones. These conclusions are also consistent with the data for the differences in pK_{BHA} for several pairs of bases shown in Table 11, the closest agreement for ΔpK_{BHA} occurring in n-heptane. The results shown in Tables 10 and 11 strongly suggest that only pK_{HBA} values obtained in aliphatic hydrocarbon, and perhaps CCl₄, solutions can be used to establish an order of acidity directly reflecting intrinsic acidities. In all other inert solvents which exhibit some basic character the results are markedly influenced by specific solvent effects involving hydrogen bonding. Even the results obtained from solutions of weakly basic inert solvents must be treated with caution, because the acid-base reaction competes with hydrogen bonding. In other words, the solvation process of the reactants and products of acid-base reactions also involves solute-solute interactions. Thus, an attempt to use the measured acid-base process as a reflection of the intrinsic acidity must also take into account hydrogen-bonded associations. An understanding of such effects can be obtained only by studying solute-solute and solvent-solvent interactions in detail and not, in general, from a measurement of an acid-base equilibrium constant.

One final point can be derived from Tables 10 and 11, viz., that the dielectric constant of the solvent is not an important factor in determining the magnitude of the equilibrium constants. In all solvents listed, the dielectric constants are well below the level where ion-pair dissociation occurs to a significant extent. Thus, for example, CCl₄ and C₆H₆ have nearly the same dielectric constant yet ΔpK_{BHA} values obtained for these solvents, where comparable results are available, show little relationship to each other; these solvents, however, are at opposite ends of the basicity scale.

B. Protophilic Solvents

It is apparent from our discussion of those substances which are conventionally described as aprotic solvents that only the aliphatic hydrocarbons and CCl₄ can be described as truly inert as

proton acceptors. All other common solvents incorporate structural features which make them more or less protophilic. Aromatic hydrocarbons and their derivatives, ethers, carbonyl-containing compounds such as ketones, esters, and N, N-dialkylacid amides are some of the classes of compounds containing protophilic moieties in their structures. The introduction of such features into solvent molecules can lead to an increase in polarity and/or dielectric constant of the molecule. Thus, the intensity and nature of the interactions of the reactants and products of an acid-base reaction with the solvent, and indirectly with each other, are affected in protophilic solvents. Consider a general acid-base reaction occurring in a protophilic solvent (Equation 34). An increase in

$$HA + B \rightleftarrows BH^+ + A^- \tag{34}$$

the dielectric constant of the solvent favors the dissociation of the salt BH^+, A^- (Equation 35), which could lead to an apparent

$$BH^+, A^- \rightleftarrows BH^+ + A^- \tag{35}$$

increase in the acidity of HA or the basicity of B. In general there is insufficient detailed information available to distinguish among the possible mechanisms which could bring about the dissociation of the salt BH^+, A^- (Equation 35) in a protophilic solvent. Ion-ion electrostatic interactions can be decreased by an increase in the dielectric constant of the solvent (Equation 23) as well as by an increase in its polarity; the former effect is dependent upon the efficiency with which charges can be screened from each other, whereas the latter effect arises from an increased ion-dipole interaction (Equation 22). Normally the dielectric and dipolar properties of solvents change more or less in the same direction, but this is not a necessary condition. For example, the dielectric constants of benzene, toluene, and triethylamine are virtually the same (Table 4) but the dipole moments of these compounds are 0.0, 0.41, and 0.61 debyes, respectively.

The specific hydrogen-bonding interactions among the species involved in acid-base reactions described in the previous section can be profoundly affected in protophilic solvents. The self-associations of bases and of acids, which occur in solvents with relatively low basicity, do not occur in solvents, such as dioxane and diethyl

ether, which are high in the basicity scale (Table 4). Again we must distinguish between the several factors which describe the nature of the solvent in considering its effect on hydrogen-bonded inter-actions. The dielectric constant and dipole mo-ment are not of primary importance, in contrast to the basicity of the solvent. The separation of hydrogen-bonded ion pairs BH^+, A^- is enhanced by an increase in the dielectric constant of the solvent even in solvents with low basicity. For example, the dissociation of the hydrogen-bonded ion pair Bu_3NH^+, Pi^- increases markedly from chlorobenzene (ϵ = 5.63, μ= 1.56D, log K = -12.68)[125] to ethylene chloride (ϵ = 10.23, μ= 1.12D, log K = -7.68).[126] If it is assumed that the difference between the basicities of these solvents is not an important factor, the increased dissociation can be attributed only to the in-crease in dielectric constant since the dipole moment of the solvent molecules decreases from chlorobenzene to ethylene chloride. On the other hand, the dissociation of the hydrogen-bonded ion pair NH_4^+ Pi^- is greater in acetone (ϵ = 20.7, μ= 2.8D, log K= -2.95)[127] than in nitrobenzene (ϵ = 38.4, μ= 3.97D, log K= -3.84)[127] even though the latter substance has both a higher dielectric con-stant and a higher dipole moment. This can only be attributed to the higher basicity of acetone as compared to nitrobenzene (Table 4) which is near that of benzene. Apparently, acetone can compete successfully with picrate ion in terms of hydrogen bonding. In systems where hydrogen bond-ing is unimportant, such as $Bu_4N^+Pi^-$ the expected order of dissociation of the ion pair is observed, i.e., log K (Acetone) = 1.65[128] and log K (nitrobenzene) = -0.7.[129] Finally, the effect of hydrogen-bonding and dielectric constant can be seen in the reaction between picric acid and aniline in nitrobenzene and acetonitrile[131] (Table 12). These two sub-stances have essentially equal dipole moments, but they have different dielectric constants and

basicities (Table 4). The dissociation process (Equation 27) occurs more readily in acetonitrile, the solvent with the higher dielectric constant, but log K_{BHA} is larger in the more basic solvent acetonitrile. It is, of course, difficult to proportion the increase in logK_{BHA} between the increase in basicity and the dielectric effect, since both factors should operate to increase the apparent acidity.

Similar considerations would be expected for the process of conjugate ion formation since hydrogen bonding is important in these species. The dissociation of conjugate cations should be enhanced in solvents of high basicity. Unfortunate-ly, only meager quantitative data are presently available to bring to bear on this point. The data in Table 13 show that the formation constants for

TABLE 13

Formation Constants[a] (25°C) for Several
Conjugate Cations Near 25°

Base	Anion[b]	K[a]	Solvent	Reference
C_5H_5N	Pi^-	56	$C_6H_5NO_2$	c,d
C_5H_5N	ClO_4^-	4	CH_3CN	e,f
C_5H_5N	Pi^-	1.9×10^4	$1,2\text{-}Cl_2C_6H_4$	g
CH_3NH_2	ClO_4^-	$10^3 - 10^4$	$C_6H_5NO_2$	h
$C_2H_5NH_2$	ClO_4^-	$10^3 - 10^4$	$C_6H_5NO_2$	h
CH_3NH_2	ClO_4^-	2	CH_3CN	e,f
$C_2H_5NH_2$	ClO_4^-	2	CH_3CN	e,f

[a]Defined as $K = BH^+ \cdot B / BH^+ \, B$
[b]Pi^- = picrate.
[c]Witschonke, C. R. and Kraus, C. A., *J. Amer. Chem., Soc.*, 69, 2471 (1947).
[d]Smyth, C. P., *Dielectric Behavior and Structure*, McGraw-Hill Book Co., New York, 1955.
[e]Muney, W. S. and Coetzee, J. F., *J. Phys. Chem.*, 66, 89 (1962).
[f]Coetzee, J. F., Padmanabhan, G. R., and Cunningham, G. P., *Talanta*, 11, 93 (1964).
[g]Ralph, E. K. III, and Gilkerson, W. R., *J. Amer. Chem. Soc.*, 86, 4783 (1964).
[h]Feakins, D., Last, W. A., and Shaw, R. A., *J. Chem. Soc.*, 2387 (1964).

TABLE 12

Log K_{BHA} and LogK_{BH^+, A^-} for Nitrobenzene and Acetonitrile Near 25°

Solvent	μ, debye	ϵ	Log K_{BHA}	Log K_{BH^+, A^-}
Nitrobenzene[a]	3.97	34.8	2.10	-4.7
Acetonitrile[b]	4.0	36.2	2.63	-2.98

[a]Witschonke, C. R. and Kraus, C. A., *J. Amer. Chem. Soc.*, 69, 2471 (1947).
[b]French, C. M. and Muggleton. D. F., *J. Chem. Soc.*, 2131 (1957).

conjugate cations in several solvents increase in the following order.

$$CH_3CN < C_6H_5NO_2 < \underline{o}\text{-}Cl_2C_6H_4$$
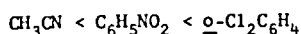
Although o-$Cl_2C_6H_4$ is not one of the solvents on the basicity scale shown in Table 4, its basicity cannot be much different from that of chlorobenzene. Thus, the order of increasing formation constants is in the reverse order of the basicities of these substances, in agreement with prediction.

C. Amphiprotic Solvents

There is no reason to suspect that the factors operative in establishing the influence of solvents on acid-base reactions in inert or protophilic solvents should not be applicable in amphiprotic solvents as well. However, there is an additional factor that must be considered in such systems, namely that the solvents can act as both a proton acceptor and donor (Equation 36). In contrast to the inert and protophilic solvents discussed

$$2 \; HS \; \rightleftharpoons \; H_2S^+ \; + \; S^- \tag{36}$$
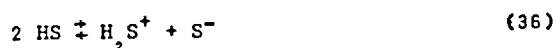
earlier, amphiprotic solvents exhibit a characteristic range within which acids and bases will be differentiated. That is, acids stronger than the solvated proton will be leveled to the strength of H_2S^+. Bases that are intrinsically stronger than the anion characteristic of the solvent, S^-, are converted to this base. Thus, the range of acid strengths which can exist in any amphiprotic solvent is governed, on the one hand, by the inherent basicity of the solvent to form H_2S^+, and on the other extreme by the inherent acidity of the solvent to form S^-. From a practical point of view the range of acidities possible in an amphiprotic solvent is measured by PK_{ion} of the solvent (Equation 37). The autoprotolysis constants, as

$$pK_{ion} = -\log[H_2S^+][S^-] \tag{37}$$

well as other characteristics, of several amphiprotic solvents are given in Table 13. In general, it appears that for amphiprotic solvents an increase in the basicity of the solvent leads to an increase in the value of PK_{ion}. Under the constraints of these assumptions, we might expect to observe a smaller range of substances acting as acids in solvents of high acidity and the range increasing for substances of lower acidity. The converse would be

true for basic solutes. It should be noted that the reference point for such statements is the autoprotolysis reaction which can be imagined as a measure of the acidity of the solvent.

Superimposed upon these considerations are the factors which were discussed previously, viz., the ability of the solvent to (1) interact in a nonspecific way to solvate dissolved species by either the dipolar (Equations 21 and 22) and/or the dielectric (Equation 23) effects or (2) undergo specific hydrogen-bonded interactions. All amphiprotic solvents have structural features that are potential hydrogen-bonding sites, which makes this effect as important in understanding acid-base behavior in these solvents as is in protophilic ones. The structural features of amphiprotic solvents also lead to highly polar molecules; increasing polarity also generally leads to a parallel increase in dielectric constant for the solvent. As is the case for protophilic solvents, the highly polar molecules do not always give solvents with proportionately greater dielectric constants. For example, the polarity of CH_3CN is larger than that of any of the substances shown in Table 14; however, its dielectric constant is smaller than that of either formic acid or water. Thus, with amphiprotic solvents, a separation of the effect of the fundamental factors influencing acid-base reactions may be difficult in the general case, although in some specific instances a reasonably complete understanding can be achieved. As a matter of convenience, water has been used as a reference solvent in discussing acid-base relationships in other solvent systems; the practice is useful from the standpoint of the number of data available for this solvent, but its large dielectric constant often masks the basis on which a thorough understanding of acid-base phenomena can be understood.

TABLE 14

The Properties of Some Amphiprotic Solvents

Solvent	pK_{ion}	μ, debye	Dielectric Constant
HCO_2H	6.67	1.35	58.5(16°)
CH_3CO_2H	12.6	1.75	6.1(20°)
H_2O	14.0	1.84	80(20°)
C^2H_5OH	19.1	1.70	24.3(25°)
CH_3OH	16.7	1.70	32.6(25°)
CH_3CN	19.5	3.97	37.5(20°)
NH_3	30	1.47	22(-33.4°)

For amphiprotic solvents it is generally difficult to relate the polarity of a solvent to its dielectric constant or basicity. Thus, formic acid and ammonia have essentially the same dipole moment, but they have markedly different dielectric constants and basic properties. Both solvents exhibit hydrogen bonding in the liquid state, so that the nature of solute-solvent interaction is difficult to elucidate. For example, although the dipole moment of HCO_2H monomer is 1.35 debye, the dimer is reported to be nonpolar[130] in the gas phase; in benzene solution the latter has a moment of 1.20 debye. [131] Even a qualitative, but unambiguous, consideration of the solvent species interacting with a given solute is impossible at present. To a first approximation, it appears that the extent to which an acid ionizes in a solvent is dependent upon the general basic properties of the solvent. Thus, the mineral acids, which behave as strong acids in aqueous solutions, can be differentiated in HCO_2H and CH_3CO_2H as solvents (Table 15), although they are completely ionized in more basic solvents. The data in Table 15 indicate that, as in other solvent systems, the order of acidity is different in these two solvents. The meager data available on the relative basicities of the same bases in both HCO_2H[132-135] and CH_3CO_2H[136-139] indicate that similar effects are operative in these systems. It is apparent that sufficient fundamental data on such systems are not available to decide whether changes in the order of acidities arises because of a difference in dielectric constants, or their solvent properties. The former certainly are important for these two solvents, since ion pairing might be an important

process in acetic acid, the solvent with the lower dielectric constant.

At the other extreme, basic solvents enhance the apparent acidities of substances. Thus, 2-nitroaniline acts as a base in acetic acid, gives essentially neutral solutions in water, but acts as an acid in liquid ammonia.[140] In this instance the widely divergent basic properties of the solvents predominate over the properties which may bear on solute-solvent effects at a lower level of interaction. Both acetic acid and ammonia have sufficiently low dielectric constants to indicate that ion association is an important process. If the solvents in question have essentially the same basicities, as for example CH_3OH, C_2H_5OH, and water, then the medium effects become predominant. Table 16 contains some representative data on the ionization of benzoic acids in the hydroxylic solvents mentioned. It is apparent from these data that the dielectric constant of solvents with similar basicity is the governing factor in determining the extents of ionization of weak acids. Indeed, there is a linear relationship between the pK_a values and the reciprocal of the dielectric constant.[141] However, even for such a simple series of solvents differences in intra- and intermolecular hydrogen bonding the neutral acid and its conjugate base must be considered to explain the fact that all of the acids do not fit the same linear relationship; in some cases an acid with a substituent in one position decreases in acidity as the dielectric constant changes, whereas an isomer will increase in acidity for the same change in dielectric constant.

Finally, it must be pointed out that even for amphiprotic solvents the interrelationship of solvent properties often causes a reversal in general trends. For example, acetonitrile and methanol have many features in common (Table 14), yet CH_3CN acts as a differentiating solvent toward the mineral acids whereas methanol does not. Acetonitrile , although it is an amphiprotic solvent (pK_{ion} = 19.5), has an interesting combination of properties which make it best discussed in terms of phenomena associated with protolytic solvents. Acetonitrile cannot form hydrogen bonds except to act as an acceptor in such bonds. The relatively low basicity of this substance, reflected by the infrared data of Table 4, is supported by thermodynamic data on phenol-base adducts.[142] The moderate dielectric constant of acetonitrile leads to low values for the dissocia-

TABLE 15

pK_a Values of Some Strong Acids in Formic Acid
and Acetic Acid Solutions

	pK_a	
Acid	HCO_2H[a]	CH_3CO_2H[b]
$HClO_4$	0.56	4.87
$p\text{-}CH_3\text{-}C_6H_4\text{-}SO_3H$	0.73	8.47
H_2SO_4	0.94	7.24
HCl	—	8.55

[a] Shkodin, A. M., *Zh. Fiz. Khim.*, 36, 595 (1962).
[b] Bruckenstein, S. and Kolthoff, I. M., *J. Amer. Chem. Soc.*, 76, 3247 (1954).

TABLE 16
The Ionization Constants of Some Acids Dissolved In
Water, Methanol, and Ethanol

Acid	pK_a H_2O (ϵ = 80 at 20°)	CH_3OH[a] (ϵ = 32.6 at 25°)	C_2H_5OH[b] (ϵ = 24.3 at 25°)
p-NO_2-C_6H_4-CO_2H	3.40	-0.47	-0.47
C_6H_5-CO_2H	4.2	0.35	0.23
p-CH_3-C_6H_4-CO_2H	4.37	0.24	0.04
p-CH_3O-C_6H_4-CO_2H	4.49	0.01	-0.16

[a] Kilpatrick, M. and Mears, W. H., *J. Amer. Chem. Soc.*, 62, 3051 (1940).
[b] Kilpatrick, M. and Mears W. H., *J. Amer. Chem. Soc.*, 62, 3047 (1940).

tion constant of typical salts (Table 3). These factors conspire to render acids less ionized in acetonitrile than in water. Indeed, the typically strong mineral acids are differentiated in acetonitrile (Table 17); protonated amines are correspondingly weaker acids in acetontitrile than in water. The low basicity of acetonitrile and its inability to act as a hydrogen-bond donor suggest that solvation effects primarily involve dipolar interactions (Equations 21,22, and 24). This com-

binatation of properties also encourages hydrogen bonding among the species in acid-base reactions. Thus, amines which bear at least one proton form homoconjugate cations (Equation 38) as do

$$BH^+ + B \rightleftarrows BH^+\cdots B \qquad (38)$$

the strong mineral acids (Equation 39) which is in keeping with the

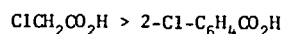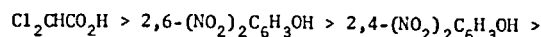$$HA + H^+ \rightleftarrows HA\cdots H^+ \qquad (39)$$

low basicity of the solvent.

As is the case in the other protophilic solvents, there is no general relationship between the relative acidity as determined in acetonitrile and any other solvent such as, for example, water. For certain classes of compounds where solvation and other factors may be relatively constant, direct relationships may be observed. For example, the equilibrium constants for carboxylic acids as determined in acetonitrile are related to those in aqueous solutions by Equation 40 which appears

$$\log K_{(CH_3CN)} = \log K_{(H_2O)} - 4.4 \qquad (40)$$

valid if hydroxy groups are not part of the structure.[143] However, for acids in general, the order of acidity is not the same in these two solvents. For example, the order in acetonitrile

$$Cl_2CHCO_2H > 2,6\text{-}(NO_2)_2C_6H_3OH > 2,4\text{-}(NO_2)_2C_6H_3OH >$$
$$ClCH_2CO_2H > 2\text{-}Cl\text{-}C_6H_4CO_2H$$

becomes, in water

$$Cl_2CHCO_2H > ClCH_2CO_2H > 2\text{-}Cl\text{-}C_6H_4CO_2H >$$
$$2,6\text{-}(NO_2)_2C_6H_3OH > 2,4\text{-}(NO_2)_2C_6H_3OH$$
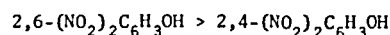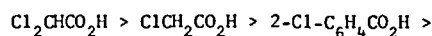
TABLE 17
pK_a Values of Several Substances in Acetonitrile and in Water

Substance	pK_a Acetonitrile	Water
HBr	5.51[a]	strong
2,5-Cl_2-C_6H_3-SO_3H	6.2 [b]	strong
H_2SO_4	7.32[a]	strong
HNO_3	8.89[a]	strong
HCl	8.94[a]	strong
HPi	11.0 [b]	0.71
CH_3SO_3H	10.0 [b]	strong
C_5H_5N	12.33[c]	5.17
2,4-$(NO_2)_2$-C_6H_3-OH	16.0 [b]	3.96
NH_3	16.46[c]	9.21
CH_3NH_2	18.37[c]	10.62
$(CH_3)_2NH$	18.73[c]	10.64
$(CH_3)_3N$	17.61[c]	9.76

[a] Kolthoff, I. M., Bruckenstein, S., and Chantooni, M. K., Jr., *J. Amer. Chem. Soc.*, 83, 3927 (1961).
[b] Kilthoff, I. M. and Chantooni, M. K., Jr., *J. Amer. Chem. Soc.*, 87, 4428 (1965).
[c] Coetzee, J. F. and Padmanabhan, G. R., *J. Amer. Chem. Soc.*, 87, 5005 (1965).

Similar results are observed among bases.[144] Many protonated simple amines are less acidic by ~ 7.6 pK_a units in acetonitrile than in water, but no general statement for all bases can be made.

VI. SUMMARY

At this point in time several major problems must be solved before the results of acid-base reactions can be predicted, even moderately well in given solvent. Theoretically, it would be desireable to be able to estimate, on the basis of energy, the intrinsic acidity of acids as well as the basicity of substances with which acids react under practical circumstances, whether the latter is a solvent or a reference base. The available data suggest that hydrogen-containing substances exhibit characteristic protonic acidities which can be manifested, more or less, in different solvents. The ionization of a substance to form protons in the gas phase is a suggested unambiguous measure of its inherent acid strength, but sufficient thermochemical data are not available to estimate the extents of such processes for a series of related compounds. The gas phase ionization can be related to the ionization process in solution by considering the solvation of the molecular form of the acid, its conjugate base, and the proton. In general, little is known of the fundamental nature of the solvation process for molecular acids and their conjugate ions, although estimates of the energy of solvation of the proton in a series of solvents, or the energy required to transfer a proton between two solvents, have been made. Perhaps the most difficult of the theoretical areas that need to be addressed is a detailed consideration of the nature of electrostatic solute-solvent interactions, as well as the more specific hydrogen-bonded interactions.

Such interactions must be better understood from a theoretical standpoint before a priori decisions can be made concerning which factors, if any, will determine the course of an acid-base reaction.

From an experimental viewpoint it appears that several general problems exist. Although a large amount of careful work is available on a few solvent systems where the relative acidities of a series of solutes have been determined by several methods, comparisons between solvents are difficult because suitable reference substances have not been included—often for no obvious reason—to allow such comparisions. In addition, measurements which purport to reflect the relative acidities of a series of compounds in a given solvent often give results that are self-consistent but are not related to the results obtained by a different method in other than qualitative way. This is, perhaps, another aspect of the problem associated with understanding solute-solvent interactions. It appears that "activity effects" are convenient receptacles of our inability to understand such interactions in detail. The existence of such problems based in a combination of theoretical interpretation and experimental technique precludes, other than in a qualitative way, even an empirical approach to the question of how the acidity of a substance changes from one solvent to the next.

Finally, there are numerous empirical relationships between the acidities of certain, rather limited, classes of compounds in different solvents; water is very often one of these solvents. Such relationships are useful for predicting, in a general way, the solvent and/or titrant that might be employed in a given analysis. Unfortunately, it is often the case that extrapolations need to be made from a solvent other than water. In such instances, the ingenuity and intuition of the chemist can be pushed to its limit.

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