8

ACIDS AND BASES

Two acid-base theories are used in organic chemistry today—the Brønsted theory and the Lewis theory.[1] These theories are quite compatible and are used for different purposes.[2]

Brønsted Theory

According to this theory, an acid is defined as a *proton donor*[3] and a base as a *proton acceptor* (a base must have a pair of electrons available to share with the proton; this is usually present as an unshared pair, but sometimes is in a π orbital). An acid-base reaction is simply the transfer of a proton from an acid to a base. (Protons do not exist free in solution but must be attached to an electron pair). When the acid gives up a proton, the species remaining still retains the electron pair to which the proton was formerly attached. Thus the new species, in theory at least, can reacquire a proton and is therefore a base. It is referred to as the *conjugate base* of the acid. All acids have a conjugate base, and all bases have a *conjugate acid*. All acid-base reactions fit the equation

$$\underset{\text{Acid}_1}{\text{A—H}} + \underset{\text{Base}_2}{\overline{\text{B}}} \rightleftharpoons \underset{\text{Base}_1}{\overline{\text{A}}} + \underset{\text{Acid}_2}{\text{B—H}}$$

No charges are shown in this equation, but an acid always has a charge one positive unit higher than that of its conjugate base.

Acid strength may be defined as the tendency to give up a proton and *base strength* as the tendency to accept a proton. Acid–base reactions occur because acids are not equally strong. If an acid, say HCl, is placed in contact with the conjugate base of a weaker acid, say acetate ion, the proton will be transferred because the HCl has a greater tendency to lose its proton than acetic acid. That is, the equilibrium

$$HCl + CH_3COO^- \rightleftharpoons CH_3COOH + Cl^-$$

lies well to the right. On the other hand, treatment of acetic acid with chloride ion gives essentially no reaction, since the weaker acid already has the proton.

This is always the case for any two acids, and by measuring the positions of the equilibrium the relative strengths of acids and bases can be determined.[4] Of course, if the two acids involved are close to each other in strength, a measurable reaction will occur from both sides, though the position of equilibrium will still be over to the side of the weaker acid

[1]For monographs on acids and bases, see Stewart *The Proton: Applications to Organic Chemistry*; Academic Press: New York, 1985; Bell *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973; Finston; Rychtman *A New View of Current Acid–Base Theories*; Wiley: New York, 1982.

[2]For discussion of the historical development of acid–base theory, see Bell *Q. Rev., Chem. Soc.* **1947**, *1*, 113-125; Bell *The Proton in Chemistry*, 1st ed.; Cornell University Press: Ithaca, NY, 1959, pp. 7-17.

[3]According to IUPAC terminology (Bunnett; Jones *Pure Appl. Chem.* **1988**, *60*, 1115), an acid is a *hydron* donor. IUPAC recommends that the term *proton* be restricted to the nucleus of the hydrogen isotope of mass 1, while the nucleus of the naturally occurring element (which contains about 0.015% deuterium) be called the *hydron* (the nucleus of mass 2 has always been known as the *deuteron*). This accords with the naturally-occurring negative ion, which has long been called the *hydride* ion. In this book, however, we will continue to use *proton* for the naturally occurring form, because most of the literature uses this term.

[4]Although equilibrium is reached in most acid–base reactions extremely rapidly (see p. 254), some are slow (especially those in which the proton is given up by a carbon) and in these cases time must be allowed for the system to come to equilibrium.

(unless the acidities are equal within experimental limits). In this manner it is possible to construct a table in which acids are listed in order of acid strength (Table 8.1).[5] Next to each acid in Table 8.1 is shown its conjugate base. It is obvious that if the acids in such a table are listed in *decreasing* order of acid strength, the bases must be listed in *increasing* order of base strength, since the stronger the acid, the weaker must be its conjugate base. The pK_a values in Table 8.1 are most accurate in the middle of the table. They are much harder to measure[6] for very strong and very weak acids, and these values must be regarded as approximate. Qualitatively, it can be determined that $HClO_4$ is a stronger acid than H_2SO_4, since a mixture of $HClO_4$ and H_2SO_4 in 4-methyl-2-pentanone can be titrated to an $HClO_4$ end point without interference by H_2SO_4.[7] Similarly, $HClO_4$ can be shown to be stronger than HNO_3 or HCl. However, this is not quantitative, and the value of -10 in the table is not much more than an educated guess. The values for RNO_2H^+, $ArNO_2H^+$, HI, $RCNH^+$ and RSH_2^+ must also be regarded as highly speculative.[8] A wide variety of pK_a values has been reported for the conjugate acids of even such simple bases as acetone[9] (-0.24 to -7.2), diethyl ether (-0.30 to -6.2), ethanol (-0.33 to -4.8), methanol (-0.34 to -4.9), and 2-propanol (-0.35 to -5.2), depending on the method used to measure them.[10] Very accurate values can be obtained only for acids weaker than hydronium ion and stronger than water.

The bottom portion of Table 8.1 consists of very weak acids[11] (pK_a above ~ 17). In most of these acids, the proton is lost from a carbon atom, and such acids are known as *carbon acids*. pK_a values for such weak acids are often difficult to measure and are known only approximately. The methods used to determine the relative positions of these acids are discussed in Chapter 5.[12] The acidity of carbon acids is proportional to the stability of the carbanions that are their conjugate bases (see p. 175).

The extremely strong acids at the top of the table are known as *super acids* (see p. 166).[13] The actual species present in the FSO_3H–SbF_5 mixture are probably $H[SbF_5(SO_3F)]$ and $H[SbF_2(SO_3F)_4]$.[14] The addition of SO_3 causes formation of the still stronger $H[SbF_4(SO_3F)_2]$, $H[SbF_3(SO_3F)_3]$, and $H[(SbF_5)_2(SO_3F)]$.[14]

By the use of tables such as Table 8.1, it is possible to determine whether a given acid will react with a given base. For tables in which acids are listed in order of decreasing strength, the rule is that *any acid will react with any base in the table that is below it but not with any above it.*[15] It must be emphasized that the order of acid strength in Table 8.1 applies

[5]Table 8.1 is a thermodynamic acidity scale and applies only to positions of equilibria. For the distinction between thermodynamic and kinetic acidity, see p. 176.

[6]For a review of methods of determining pK_a values, see Cookson *Chem. Rev.* **1974**, *74*, 5-28.

[7]Kolthoff; Bruckenstein, in Kolthoff; Elving *Treatise on Analytical Chemistry*, vol. 1, pt. 1; Wiley: New York, 1959, pp. 475-542, p. 479.

[8]For reviews of organic compounds protonated at O, N, or S, see Olah; White; O'Brien *Chem. Rev.* **1970**, *70*, 561-591; Olah; White; O'Brien, in Olah; Schleyer *Carbonium Ions*, vol. 4; Wiley: New York, 1973, pp. 1697-1781.

[9]For discussions of pK_a determinations for the conjugate acids of ketones, see Bagno; Lucchini; Scorrano *Bull. Soc. Chim. Fr.* **1987**, 563; Toullec *Tetrahedron Lett.* **1988**, *29*, 5541.

[10]Rochester *Acidity Functions*; Academic Press: New York, 1970. For discussion of the basicity of such compounds, see Liler *Reaction Mechanisms in Sulfuric Acid*; Academic Press: New York, 1971, pp. 118-139.

[11]For a monograph on very weak acids, see Reutov; Beletskaya; Butin *CH-Acids*; Pergamon: New York, 1978. For other discussions, see Cram *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965, pp. 1-45; Streitwieser; Hammons *Prog. Phys. Org. Chem.* **1965**, *3*, 41-80.

[12]For reviews of methods used to measure the acidity of carbon acids, see Jones *Q. Rev., Chem. Soc.* **1971**, *25*, 365-378; Fischer; Rewicki *Prog. Org. Chem.* **1968**, *7*, 116-161; Reutov; Beletskaya; Butin, Ref. 11, Chapter 1 [an earlier version of this chapter appeared in *Russ. Chem. Rev.* **1974**, *43*, 17-31]; Ref. 6. For reviews on acidities of carbon acids, see Gau; Assadourian; Veracini *Prog. Phys. Org. Chem.* **1987**, *16*, 237-285; in Buncel; Durst *Comprehensive Carbanion Chemistry*, pt. A; Elsevier: New York, 1980, the reviews by Pellerite; Brauman, pp. 55-96 (gas phase acidities); and Streitwieser; Juaristi; Nebenzahl, pp. 323-381.

[13]For a monograph, see Olah; Prakash; Sommer *Superacids*; Wiley: New York, 1985. For a review, see Gillespie; Peel *Adv. Phys. Org. Chem.* **1971**, *9*, 1-24. For a review of solid superacids, see Arata *Adv. Catal.* **1990**, *37*, 165-211. For a review of methods of measuring superacidity, see Jost; Sommer *Rev. Chem. Intermed.* **1988**, *9*, 171-199.

[14]Gillespie *Acc. Chem. Res.* **1968**, *1*, 202-209.

[15]These reactions are equilibria. What the rule actually says is that the position of equilibrium will be such that the weaker acid predominates. However, this needs to be taken into account only when the acid and base are close to each other in the table (within about 2 pK units).

TABLE 8.1 pK_a values for many types of acids

The values in boldface are exact values; the others are approximate, especially above 18 and below −2[16]

Acid	Base	Approximate pK_a (relative to water)	Ref.
Super acids:			
$HF\text{–}SbF_5$	SbF_6^-		19
$FSO_3H\text{–}SbF_5\text{–}SO_3$			14
$FSO_3H\text{–}SbF_5$			14, 19
FSO_3H	FSO_3^-		14
RNO_2H^+	RNO_2	−12	20
$ArNO_2H^+$	$ArNO_2$	−11	20
$HClO_4$	ClO_4^-	−10	21
HI	I^-	−10	21
$RCNH^+$	RCN	−10	22
R—C(=OH$^+$)—H	R—C(=O)—H	−10	23
H_2SO_4	HSO_4^-		
HBr	Br^-	−9	21
Ar—C(=OH$^+$)—OR[17]	Ar—C(=O)—OR	−7.4	20
HCl	Cl^-	−7	21
RSH_2^+	RSH	−7	20
Ar—C(=OH$^+$)—OH[17]	Ar—C(=O)—OH	−7	24
Ar—C(=OH$^+$)—H	Ar—C(=O)—H	−7	25
R—C(=OH$^+$)—R	R—C(=O)—R	−7	9, 22, 26
$ArSO_3H$	$ArSO_3^-$	−6.5	27
R—C(=OH$^+$)—OR[17]	R—C(=O)—OR	−6.5	20
$ArOH_2^+$	$ArOH$	−6.4	28
R—C(=OH$^+$)—OH[17]	R—C(=O)—OH	−6	20
Ar—C(=OH$^+$)—R	Ar—C(=O)—R	−6	25, 29
Ar—O$^+$(H)—R	Ar—O—R	−6	28, 30
$CH(CN)_3$	$^-C(CN)_3$	−5	31
Ar_3NH^+	Ar_3N	−5	32
H—C(=OH$^+$)—H	H—C(=O)—H	−4	33
R—O$^+$(H)—R	R—O—R	−3.5	22, 30, 34
$R_3COH_2^+$	R_3COH	−2	34
$R_2CHOH_2^+$	R_2CHOH	−2	34, 35
$RCH_2OH_2^+$	RCH_2OH	−2	22, 34, 35
H_3O^+	H_2O	**−1.74**	36

TABLE 8.1 *(Continued)*

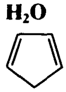
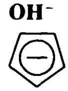
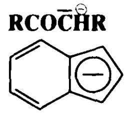
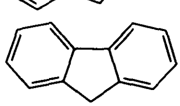
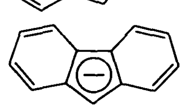
Acid	Base	Approximate pK_a (relative to water)	Ref.
$Ar{-}C({=}OH^+){-}NH_2$ [17]	$Ar{-}C({=}O){-}NH_2$	−1.5	37
HNO_3	NO_3^-	−1.4	21
$R{-}C({=}OH^+){-}NH_2$ [17]	$R{-}C({=}O){-}NH_2$	−0.5	37
$Ar_2NH_2^+$	Ar_2NH	1	32
HSO_4^-	SO_4^{2-}	**1.99**	38
HF	F^-	**3.17**	38
HONO	NO_2^-	**3.29**	38
$ArNH_3^+$	$ArNH_2$	3–5	39
$ArNR_2H^+$	$ArNR_2$	3–5	39
RCOOH	$RCOO^-$	4–5	39
$HCOCH_2CHO$	$HCO\overset{\ominus}{\bar{C}}HCHO$	5	40
H_2CO_3 [18]	HCO_3^-	**6.35**	38
H_2S	HS^-	**7.00**	38
ArSH	ArS^-	6–8	41
$CH_3COCH_2COCH_3$	$CH_3CO\overset{\ominus}{\bar{C}}HCOCH_3$	9	40
HCN	CN^-	9.2	42
NH_4^+	NH_3	**9.24**	38
ArOH	ArO^-	8–11	43
RCH_2NO_2	$R\overset{\ominus}{\bar{C}}HNO_2$	10	44
R_3NH^+	R_3N	10–11	39
RNH_3^+	RNH_2	10–11	39
HCO_3^-	CO_3^{2-}	**10.33**	38
RSH	RS^-	10–11	41
$R_2NH_2^+$	R_2NH	11	39
$NCCH_2CN$	$NC\overset{\ominus}{\bar{C}}HCN$	11	40, 45
CH_3COCH_2COOR	$CH_3CO\overset{\ominus}{\bar{C}}HCOOR$	11	40
$CH_3SO_2CH_2SO_2CH_3$	$CH_3SO_2\overset{\ominus}{\bar{C}}HSO_2CH_3$	12.5	46
$EtOOCCH_2COOEt$	$EtOOC\overset{\ominus}{\bar{C}}HCOOEt$	13	40
CH_3OH	CH_3O^-	15.2	47, 48
H_2O	OH^-	**15.74**	49
		16	50
RCH_2OH	RCH_2O^-	16	47
RCH_2CHO	$R\overset{\ominus}{\bar{C}}HCHO$	16	51
R_2CHOH	R_2CHO^-	16.5	47
R_3COH	R_3CO^-	17	47
$RCONH_2$	$RCONH^-$	17	52
$RCOCH_2R$	$RCO\overset{\ominus}{\bar{C}}HR$	19–20	53
		20	54, 55
		23	54, 55
$ROOCCH_2R$	$ROOC\overset{\ominus}{\bar{C}}HR$	24.5	40

TABLE 8.1 (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	Ref.
RCH_2CN	$R\bar{C}HCN$	25	40, 56
$HC{\equiv}CH$	$HC{\equiv}C^-$	25	57
Ar_3CH	Ar_3C^-	31.5	54, 58
Ar_2CH_2	Ar_2CH^-	33.5	54, 58
H_2	H^-	35	59
NH_3	NH_2^-	38	60
$PhCH_3$	$PhCH_2^-$	40	61
$CH_2{=}CHCH_3$	$[CH_2{\cdots}CH{\cdots}CH_2]^-$	43	62
PhH	Ph^-	43	63
$CH_2{=}CH_2$	$CH_2{=}CH^-$	44	64
cyclo-C_3H_6	cyclo-$C_3H_5^-$	46	65
CH_4	CH_3^-	48	66
C_2H_6	$C_2H_5^-$	50	67
$(CH_3)_2CH_2$	$(CH_3)_2CH^-$	51	67
$(CH_3)_3CH$	$(CH_3)_3C^-$	—	68

[16]In this table we do not give pK_a values for individual compounds (with a few exceptions), only average values for functional groups. Extensive tables of pK values for many carboxylic and other acids and amines are given in Ref. 39. Values for more than 5500 organic acids are given in Serjeant; Dempsey *Ionisation Constants of Organic Acids in Aqueous Solution*; Pergamon: Elmsford, NY, 1979; Kortüm; Vogel; Andrussow *Dissociation Constants of Organic Acids in Aqueous Solution*; Butterworth: London, 1961. The index in the 1979 volume covers both volumes. Kortüm; Vogel; Andrussow *Pure Appl. Chem.* **1960,** *1*, 190-536 give values for 631 carboxylic acids and 110 phenols. Ref. 20 gives hundreds of values for very strong acids (very weak bases). Perrin *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworth: London, 1965, and Supplement, 1972 list pK values for more than 7000 amines and other bases. Collumeau *Bull. Soc. Chim. Fr.* **1968,** 5087-5112 gives pK values for about 800 acids and bases. Bordwell *Acc. Chem. Res.* **1988,** *21*, 456-463 gives values for more than 300 acids in dimethyl sulfoxide. For inorganic acids and bases, see Perrin, Ref. 42, *Pure Appl. Chem.* **1969,** *20*, 133-236.

[17]Carboxylic acids, esters, and amides are shown in this table to be protonated on the carbonyl oxygen. There has been some controversy on this point, but the weight of evidence is in that direction. See, for example, Katritzky; Jones *Chem. Ind. (London)* **1961,** 722; Ottenheym; van Raayen; Smidt; Groenewege; Veerkamp *Recl. Trav. Chim. Pays-Bas* **1961,** *80*, 1211; Stewart; Muenster *Can. J. Chem.* **1961,** *39*, 401; Smith; Yates *Can. J. Chem.* **1972,** *50*, 771; Benedetti; Di Blasio; Baine *J. Chem. Soc. Perkin Trans. 2* **1980,** 500; Ref. 8; Homer; Johnson, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 188-197. It has been shown that some amides protonate at nitrogen: see Perrin *Acc. Chem. Res.* **1989,** *22*, 268-275. For a review of alternative proton sites, see Liler *Adv. Phys. Org. Chem.* **1975,** *11*, 267-392.

[18]This value includes the CO_2 usually present. The value for H_2CO_3 alone is 3.9 (Ref. 21).

[19]Brouwer; van Doorn *Recl. Trav. Chim. Pays-Bas* **1972,** *91*, 895; Gold; Laali; Morris; Zdunek *J. Chem. Soc., Chem. Commun.* **1981,** 769; Sommer; Canivet; Schwartz; Rimmelin *Nouv. J. Chim.* **1981,** *5*, 45.

[20]Arnett *Prog. Phys. Org. Chem.* **1963,** *1*, 223-403, pp. 324-325.

[21]Bell, Ref. 1.

[22]Deno; Wisotsky *J. Am. Chem. Soc.* **1963,** *85*, 1735; Deno; Gaugler; Wisotsky *J. Org. Chem.* **1966,** *31*, 1967.

[23]Levy; Cargioli; Racela *J. Am. Chem. Soc.* **1970,** *92*, 6238. See, however, Brouwer; van Doorn *Recl. Trav. Chim. Pays-Bas* **1971,** *90*, 1010.

[24]Stewart; Granger *Can. J. Chem.* **1961,** *39*, 2508.

[25]Yates; Stewart *Can. J. Chem.* **1959,** *37*, 664; Stewart; Yates *J. Am. Chem. Soc.* **1958,** *80*, 6355.

[26]Lee *Can. J. Chem.* **1970,** *48*, 1919.

[27]Cerfontain; Koeberg-Telder; Kruk *Tetrahedron Lett.* **1975,** 3639.

[28]Arnett; Wu *J. Am. Chem. Soc.* **1960,** *82*, 5660; Koeberg-Telder; Lambrechts; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1983,** *102*, 293.

[29]Fischer; Grigor; Packer; Vaughan *J. Am. Chem. Soc.* **1961,** *83*, 4208.

[30]Arnett; Wu *J. Am. Chem. Soc.* **1960,** *82*, 4999.

[31]Boyd *J. Phys. Chem.* **1963,** *67*, 737.

[32]Arnett; Quirk; Burke *J. Am. Chem. Soc.* **1970,** *92*, 1260.

[33]McTigue; Sime *Aust. J. Chem.* **1963,** *16*, 592.

[34]Deno; Turner *J. Org. Chem.* **1966,** *31*, 1969.

[35]Lee; Demchuk *Can. J. Chem.* **1987,** *65*, 1769; Chandler; Lee *Can. J. Chem.* **1990,** *68*, 1757.

[36]For a discussion, see Campbell; Waite *J. Chem. Educ.* **1990,** *67*, 386.

[37]Cox; Druet; Klausner; Modro; Wan; Yates *Can. J. Chem.* **1981,** *59*, 1568; Grant; McTigue; Ward *Aust. J. Chem.* **1983,** *36*, 2211.

when a given acid and base react without a solvent or, when possible, in water. In other solvents the order may be greatly different (see p. 272). In the gas phase, where solvation effects are completely or almost completely absent, acidity orders may also differ greatly.[69] For example, in the gas phase, toluene is a stronger acid than water and *t*-butoxide ion is a weaker base than methoxide ion[70] (see also pp. 270-272). It is also possible for the acidity order to change with temperature. For example, above 50°C the order of base strength is BuOH > H_2O > Bu_2O; from 1 to 50°C the order is BuOH > Bu_2O > H_2O; while below 1°C the order becomes Bu_2O > BuOH > H_2O.[71]

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[38]Bruckenstein; Kolthoff; in Kolthoff; Elving *Treatise on Analytical Chemistry*, vol. 1, pt. 1; Wiley: New York, 1959, pp. 432-433.

[39]Brown; McDaniel; Häflinger, in Braude; Nachod *Determination of Organic Structures by Physical Methods*, vol. 1; Academic Press: New York, 1955, pp. 567-662.

[40]Pearson; Dillon *J. Am. Chem. Soc.* **1953,** *75*, 2439.

[41]Crampton, in Patai *The Chemistry of the Thiol Group*, pt. 1; Wiley: New York, 1974, pp. 396-410.

[42]Perrin *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed.; Pergamon: Elmsford, NY, 1982.

[43]Rochester, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, p. 374.

[44]Cram *Chem. Eng. News* **1963,** *41*(No. 33, Aug. 19), 94.

[45]Bowden; Stewart *Tetrahedron* **1965,** *21*, 261.

[46]Hine; Philips; Maxwell *J. Org. Chem.* **1970,** *35*, 3943. See also Ang; Lee *Aust. J. Chem.* **1977,** *30*, 521.

[47]Reeve; Erikson; Aluotto *Can. J. Chem.* **1979,** *57*, 2747.

[48]See also Mackay; Bohme *J. Am. Chem. Soc.* **1978,** *100*, 327; Olmstead; Margolin; Bordwell *J. Org. Chem.* **1980,** *45*, 3295.

[49]Harned; Robinson *Trans. Faraday Soc.* **1940,** *36*, 973.

[50]Streitwieser; Nebenzahl *J. Am. Chem. Soc.* **1976,** *98*, 2188.

[51]Guthrie; Cossar *Can. J. Chem.* **1986,** *64*, 2470.

[52]Homer; Johnson, Ref. 17, pp. 238-240.

[53]Tapuhi; Jencks *J. Am. Chem. Soc.* **1982,** *104*, 5758; Guthrie; Cossar; Klym *J. Am. Chem. Soc.* **1984,** *106*, 1351; Chiang; Kresge; Tang; Wirz *J. Am. Chem. Soc.* **1984,** *106*, 460.

[54]Streitwieser; Ciuffarin; Hammons *J. Am. Chem. Soc.* **1967,** *89*, 63.

[55]Streitwieser; Hollyhead; Pudjaatmaka; Owens; Kruger; Rubenstein; MacQuarrie; Brokaw; Chu; Niemeyer *J. Am. Chem. Soc.* **1971,** *93*, 5088.

[56]For a review of the acidity of cyano compounds, see Hibbert, in Patai; Rappoport *The Chemistry of Triple-bonded Functional Groups*, pt. 1; Wiley: New York, 1983, pp. 699-736.

[57]Cram, Ref. 11, p. 19. See also Dessy; Kitching; Psarras; Salinger; Chen; Chivers *J. Am. Chem. Soc.* **1966,** *88*, 460.

[58]Streitwieser; Hollyhead; Sonnichsen; Pudjaatmaka; Chang; Kruger *J. Am. Chem. Soc.* **1971,** *93*, 5096.

[59]Buncel; Menon *J. Am. Chem. Soc.* **1977,** *99*, 4457.

[60]Buncel; Menon *J. Organomet. Chem.* **1977,** *141*, 1.

[61]Streitwieser; Ni *Tetrahedron Lett.* **1985,** *26*, 6317; Albrecht; Schneider *Tetrahedron* **1986,** *42*, 4729.

[62]Boerth; Streitwieser *J. Am. Chem. Soc.* **1981,** *103*, 6443.

[63]Streitwieser; Scannon; Niemeyer *J. Am. Chem. Soc.* **1972,** *94*, 7936.

[64]Maskornick; Streitwieser *Tetrahedron Lett.* **1972,** 1625; Streitwieser; Boerth *J. Am. Chem. Soc.* **1978,** *100*, 755.

[65]This value is calculated from results given in Streitwiesser; Caldwell; Young *J. Am. Chem. Soc.* **1969,** *91*, 529. For a review of acidity and basicity of cyclopropanes, see Battiste; Coxon, in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley: New York, 1987, pp. 255-305.

[66]This value is calculated from results given in Streitwieser; Taylor *J. Chem. Soc. D* **1970,** 1248.

[67]These values are based on those given in Ref. 44 but are corrected to the newer scale of Streitwieser; Refs. 63 and 64.

[68]Breslow and co-workers report a value of 71 [Breslow; Goodin *J. Am. Chem. Soc.* **1976,** *98*, 6076; Breslow; Grant *J. Am. Chem. Soc.* **1977,** *99*, 7745], but this was obtained by a different method, and is not comparable to the other values in Table 8.1. A more comparable value is about 53. See also Juan; Schwarz; Breslow *J. Am. Chem. Soc.* **1980,** *102*, 5741.

[69]For a review of acidity and basicity scales in the gas phase and in solution, see Gal; Maria *Prog. Phys. Org. Chem.* **1990,** *17*, 159-238.

[70]Brauman; Blair *J. Am. Chem. Soc.* **1970,** *92*, 5986; Bohme; Lee-Ruff; Young *J. Am. Chem. Soc.* **1972,** *94*, 4608, 5153.

[71]Gerrard; Macklen *Chem. Rev.* **1959,** *59*, 1105-1123. For other examples, see Calder; Barton *J. Chem. Educ.* **1971,** *48*, 338; Hambly *Rev. Pure Appl. Chem.* **1965,** *15*, 87-100, p. 88.

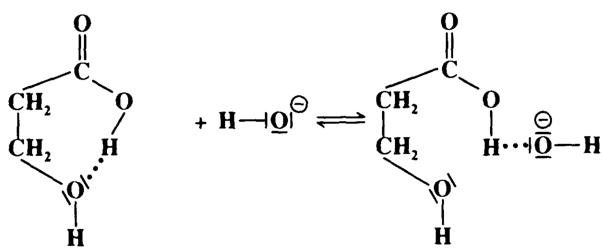
The Mechanism of Proton Transfer Reactions

Proton transfers between oxygen and nitrogen acids and bases are usually extremely fast.[72] In the thermodynamically favored direction they are generally diffusion controlled.[73] In fact, a *normal acid* is defined[74] as one whose proton transfer reactions are completely diffusion controlled, except when the conjugate acid of the base to which the proton is transferred has a p*K* value very close (differs by < about 2 p*K* units) to that of the acid. The normal acid–base reaction mechanism consists of three steps:

1. **HA + |B ⇌ AH···|B**
2. **AH···|B ⇌ A|···HB**
3. **A|···HB ⇌ A| + HB**

The actual proton transfer takes place in the second step—the first step is formation of a hydrogen-bonded complex. The product of the second step is another hydrogen-bonded complex, which dissociates in the third step.

However, not all such proton transfers are diffusion controlled. For example, if an internal hydrogen bond exists in a molecule, reaction with an external acid or base is often much slower.[75] In a case such as this:



3 - Hydroxypropanoic acid

the OH^- ion can form a hydrogen bond with the acidic hydrogen only if the internal hydrogen bond breaks. Therefore only some of the collisions between OH^- ions and 3-hydroxypropanoic acid molecules result in proton transfer. In many collisions the OH^- ions will come away empty-handed, resulting in a lower reaction rate. Note that this affects only the rate, not the equilibrium. Another factor that can create lower rates is a molecular structure in which the acidic proton is protected within a molecular cavity (e.g., the in–in and out–in isomers shown on p. 133). See also the proton sponges mentioned on p. 268. Proton transfers between an acidic and a basic group within the same molecule can also be slow, if the two groups are too far apart for hydrogen bonding. In such cases participation of solvent molecules may be necessary.

[72]For reviews of such proton transfers, see Hibbert *Adv. Phys. Org. Chem.* **1986,** *22,* 113-212; Crooks, in Bamford; Tipper *Chemical Kinetics*, vol. 8; Elsevier: New York, 1977, pp. 197-250.

[73]Kinetic studies of these very fast reactions were first carried out by Eigen. See Eigen *Angew. Chem. Int. Ed. Engl.* **1964,** *3,* 1-19 [*Angew. Chem.* **1963,** *75,* 489-509].

[74]See, for example, Hojatti; Kresge; Wang *J. Am. Chem. Soc.* **1987,** *109,* 4023.

[75]For an example of a slow proton transfer from F_3CCOOH to $(PhCH_2)_3N$, see Ritchie; Lu *J. Am. Chem. Soc.* **1989,** *111,* 8542.

Proton transfers to or from a carbon atom[76] in most cases are much slower than those strictly between oxygen or nitrogen atoms. At least three factors can be responsible for this,[77] not all of them applying in every case:

1. Hydrogen bonding is very weak or altogether absent for carbon (Chapter 3).

2. Many carbon acids, upon losing the proton, form carbanions that are stabilized by resonance. Structural reorganization (movement of atoms to different positions within the molecule) may accompany this. Chloroform, HCN, and 1-alkynes do not form resonance-stabilized carbanions, and these[78] behave kinetically as normal acids.[79]

3. There may be considerable reorganization of solvent molecules around the ion as compared to the neutral molecule.[80]

In connection with factors 2 and 3, it has been proposed[77] that any factor that stabilizes the product (e.g., by resonance or solvation) lowers the rate constant if it develops late on the reaction coordinate, but increases the rate constant if it develops early. This is called the Principle of Imperfect Synchronization.

Measurements of Solvent Acidity[81]

When a solute is added to an acidic solvent it may become protonated by the solvent. If the solvent is water and the concentration of solute is not very great, then the pH of the solution is a good measure of the proton-donating ability of the solvent. Unfortunately, this is no longer true in concentrated solutions because activity coefficients are no longer unity. A measurement of solvent acidity is needed which works in concentrated solutions and applies to mixed solvents as well. The Hammett acidity function[82] is a measurement that is used for acidic solvents of high dielectric constant.[83] For any solvent, including mixtures of solvents (but the proportions of the mixture must be specified), a value H_0 is defined as

$$H_0 = pK_{BH_w^+} - \log \frac{[BH^+]}{[B]}$$

H_0 is measured by using "indicators" that are weak bases (B) and so are partly converted, in these acidic solvents, to the conjugate acids BH^+. Typical indicators are *o*-nitroanilinium ion, with a pK in water of -0.29, and 2,4-dinitroanilinium ion, with a pK in water of -4.53. For a given solvent, $[BH^+]/[B]$ is measured for one indicator, usually by spectrophotometric means. Then, using the known pK in water ($pK_{BH_w^+}$) for that indicator, H_0 can be calculated for that solvent system. In practice, several indicators are used, so that an average H_0 is

[76]For reviews of proton transfers to and from carbon, see Hibbert, in Bamford; Tipper, Ref. 72, pp. 97-196; Kreevoy *Isot. Org. Chem.* **1976,** *2*, 1-31; Leffek *Isot. Org. Chem.* **1976,** *2*, 89-125.

[77]See Bernasconi *Tetrahedron* **1985,** *41*, 3219.

[78]Lin; Chiang; Dahlberg; Kresge *J. Am. Chem. Soc.* **1983,** *105*, 5380; Bednar; Jencks *J. Am. Chem. Soc.* **1985,** *107*, 7117, 7126, 7135; Kresge; Powell *J. Org. Chem.* **1986,** *51*, 822; Formosinho; Gal *J. Chem. Soc., Perkin Trans. 2* **1987,** 1655.

[79]Not all 1-alkynes behave as normal acids; see Aroella; Arrowsmith; Hojatti; Kresge; Powell; Tang; Wang *J. Am. Chem. Soc.* **1987,** *109*, 7198.

[80]See Bernasconi; Terrier *J. Am. Chem. Soc.* **1987,** *109*, 7115; Kurz *J. Am. Chem. Soc.* **1989,** *111*, 8631.

[81]For fuller treatments, see Hammett *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970, pp. 263-313; Jones *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1984, pp. 83-93; Arnett; Scorrano *Adv. Phys. Org. Chem.* **1976,** *13*, 83-153.

[82]Hammett; Deyrup *J. Am. Chem. Soc.* **1932,** *54*, 2721.

[83]For a monograph on acidity functions, see Rochester, Ref. 10. For reviews, see Ref. 81; Cox; Yates *Can. J. Chem.* **1983,** *61*, 2225-2243; Boyd, in Coetzee; Ritchie *Solute-Solvent Interactions*; Marcel Dekker: New York, 1969, pp. 97-218; Vinnik *Russ. Chem. Rev.* **1966,** *35*, 802-817; Liler, Ref. 10, pp. 26-58.

taken. Once H_0 is known for a given solvent system, pK_a values in it can be calculated for any other acid–base pair.

The symbol h_0 is defined as

$$h_0 = \frac{a_{H^+} f_I}{f_{HI^+}}$$

where a_{H^+} is the activity of the proton and f_I and f_{HI^+} are the activity coefficients of the indicator and conjugate acid of the indicator,[84] respectively. H_0 is related to h_0 by

$$H_0 = -\log h_0$$

so that H_0 is analogous to pH and h_0 to $[H^+]$, and indeed in dilute aqueous solution H_0 = pH.

H_0 reflects the ability of the solvent system to donate protons, but it can be applied only to acidic solutions of high dielectric constant, mostly mixtures of water with acids such as nitric, sulfuric, perchloric, etc. It is apparent that the H_0 treatment is valid only when f_I/f_{HI^+} is independent of the nature of the base (the indicator). Since this is so only when the bases are structurally similar, the treatment is limited. Even when similar bases are compared, many deviations are found.[85] Other acidity scales[86] have been set up, among them H_- for bases with a charge of -1, H_R for aryl carbinols,[87] H_C for bases that protonate on carbon,[88] and H_A for unsubstituted amides.[89] It is now clear that there is no single acidity scale that can be applied to a series of solvent mixtures, irrespective of the bases employed.[90]

Although most acidity functions have been applied only to acidic solutions, some work has also been done with strongly basic solutions.[91] The H_- function, which is used for highly acidic solutions when the base has a charge of -1, can also be used for strongly basic solvents, in which case it measures the ability of these solvents to abstract a proton from a neutral acid BH.[92] When a solvent becomes protonated, its conjugate acid is known as a *lyonium ion*.

Another approach to the acidity function problem was proposed by Bunnett and Olsen,[93] who derived the equation

$$\log \frac{[\mathbf{SH^+}]}{[\mathbf{S}]} + H_0 = \phi(H_0 + \log [\mathbf{H}^+]) + pK_{SH^+}$$

[84]For a review of activity coefficient behavior of indicators in acid solutions, see Yates; McClelland *Prog. Phys. Org. Chem.* **1974,** *11*, 323-420.

[85]For example, see Kresge; Barry; Charles; Chiang *J. Am. Chem. Soc.* **1962,** *84*, 4343; Katritzky; Waring; Yates *Tetrahedron* **1963,** *19*, 465; Arnett; Mach *J. Am. Chem. Soc.* **1964,** *86*, 2671; Jorgenson; Hartter *J. Am. Chem. Soc.* **1963,** *85*, 878; Kreevoy; Baughman *J. Am. Chem. Soc.* **1973,** *95*, 8178; García; Leal; Herrero; Palacios *J. Chem. Soc., Perkin Trans. 2* **1988,** 1759; Ref. 32.

[86]For lengthy tables of many acidity scales, with references, see Cox; Yates, Ref. 83. For an equation that is said to combine the vast majority of acidity functions, see Zalewski; Sarkice; Geltz *J. Chem. Soc., Perkin Trans. 2* **1983,** 1059.

[87]Deno; Jaruzelski; Schriesheim *J. Am. Chem. Soc.* **1955,** *77*, 3044; Deno; Berkheimer; Evans; Peterson *J. Am. Chem. Soc.* **1959,** *81*, 2344.

[88]Reagan *J. Am. Chem. Soc.* **1969,** *91*, 5506.

[89]Yates; Stevens; Katritzky *Can. J. Chem.* **1964,** *42*, 1957; Yates; Riordan *Can. J. Chem.* **1965,** *43*, 2328; Edward; Wong *Can. J. Chem.* **1977,** *55*, 2492; Liler; Marković *J. Chem. Soc., Perkin Trans. 2* **1982,** 551.

[90]Hammett, Ref. 81, p. 278; Rochester, Ref. 10, p. 21.

[91]For another approach to solvent basicity scales, see Catalán; Gómez; Couto; Laynez *J. Am. Chem. Soc.* **1990,** *112*, 1678.

[92]For reviews, see Rochester *Q. Rev., Chem. Soc.* **1966,** *20*, 511-525; Rochester, Ref. 10, pp. 234-264; Bowden *Chem. Rev.* **1966,** *66*, 119-131 (the last review is reprinted in Coetzee and Ritchie, Ref. 83, pp. 186-215).

[93]Bunnett; Olsen *Can. J. Chem.* **1966,** *44*, 1899, 1917; Bunnett; McDonald; Olsen *J. Am. Chem. Soc.* **1974,** *96*, 2855.

where S is a base that is protonated by an acidic solvent. Thus the slope of a plot of log ($[SH^+]/[S]$) + H_0 against H_0 + log $[H^+]$ is the parameter ϕ, while the intercept is the pK_a of the lyonium ion SH^+ (referred to infinite dilution in water). The value of ϕ expresses the response of the equilibrium $S + H^+ \rightleftharpoons SH^+$ to changing acid concentration. A negative ϕ indicates that the log of the ionization ratio $[SH^+]/[S]$ increases, as the acid concentration increases, more rapidly than $-H_0$. A positive ϕ value indicates the reverse. The Bunnett–Olsen equation given above is a linear free-energy relationship (see p. 281) that pertains to acid-base equilibria. A corresponding equation that applies to kinetic data is

$$\log k_\psi + H_0 = \phi(H_0 + \log [\mathbf{H}^+]) + \log k_2^\circ$$

where k_ψ is the pseudo-first-order rate constant for a reaction of a weakly basic substrate taking place in an acidic solution and k_2° is the second-order rate constant at infinite dilution in water. In this case ϕ characterizes the response of the reaction rate to changing acid concentration of the solvent. The Bunnett–Olsen treatment has also been applied to basic media, where, in a group of nine reactions in concentrated NaOMe solutions, no correlation was found between reaction rates and either H_- or stoichiometric base concentration but where the rates were successfully correlated by a linear free-energy equation similar to those given above.[94]

A treatment partially based on the Bunnett–Olsen one is that of Bagno, Scorrano, and More O'Ferrall,[95] which formulates medium effects (changes in acidity of solvent) on acid–base equilibria. An appropriate equilibrium is chosen as reference, and the acidity dependence of other reactions compared with it, by use of the linear free-energy equation

$$\log \frac{K'}{K_0'} = m^* \log \frac{K}{K_0}$$

where the K values are the equilibrium constants for the following:

K for the reaction under study in any particular medium
K' for the reference reaction in the same medium
K_0 for the reaction under study in a reference solvent
K_0' for the reference reaction in the same reference solvent

and m^* is the slope of the relationship [corresponding to $(1 - \phi)$ of the Bunnett–Olsen treatment]. This equation has been shown to apply to many acid–base reactions.

Another type of classification system was devised by Bunnett[96] for reactions occurring in moderately concentrated acid solutions. Log $k_\psi + H_0$ is plotted against log a_{H_2O}, where K_ψ is the pseudo-first-order rate constant for the protonated species and a_{H_2O} is the activity of water. Most such plots are linear or nearly so. According to Bunnett, the slope of this plot w tells something about the mechanism. Where w is between -2.5 and 0, water is not involved in the rate-determining step; where w is between 1.2 and 3.3, water is a nucleophile in the rate-determining step; where w is between 3.3 and 7, water is a proton-transfer agent. These rules hold for acids in which the proton is attached to oxygen or nitrogen.

[94]More O'Ferrall *J. Chem. Soc., Perkin Trans. 2* **1972,** 976.
[95]Bagno; Scorrano; More O'Ferrall *Rev. Chem. Intermed.* **1987,** *7,* 313-352. See also Marziano; Cimino; Passerini *J. Chem. Soc., Perkin Trans. 2* **1973,** 1915; Lucchini; Modena; Scorrano; Cox; Yates *J. Am. Chem. Soc.* **1982,** *104,* 1958; Sampoli; De Santis; Marziano *J. Chem. Soc., Chem. Commun.* **1985,** 110; Cox *Acc. Chem. Res.* **1987,** *20,* 27-31.
[96]Bunnett *J. Am. Chem. Soc.* **1961,** *83,* 4956, 4968, 4973, 4978.

Acid and Base Catalysis[97]

Many reactions are catalyzed by acids, bases, or both. In such cases the catalyst is involved in a fundamental way in the mechanism. Nearly always the first step of such a reaction is a proton transfer between the catalyst and the substrate.

Reactions can be catalyzed by acid or base in two different ways, called *general* and *specific catalysis*. If the rate of an acid-catalyzed reaction run in a solvent S is proportional to $[SH^+]$, the reaction is said to be subject to *specific acid catalysis*, the acid being the lyonium ion SH^+. The acid that is put into the solvent may be stronger or weaker than SH^+, but the rate is proportional only to the $[SH^+]$ that is actually present in the solution (derived from $S + HA \rightleftharpoons SH^+ + A^-$). The identity of HA makes no difference except insofar as it determines the position of equilibrium and hence the $[SH^+]$. Most measurements have been made in water, where SH^+ is H_3O^+.

In *general acid catalysis*, the rate is increased not only by an increase in $[SH^+]$ but also by an increase in the concentration of other acids (e.g., in water by phenols or carboxylic acids). These other acids increase the rate even when $[SH^+]$ is held constant. In this type of catalysis the strongest acids catalyze best, so that, in the example given, an increase in the phenol concentration catalyzes the reaction much less than a similar increase in $[H_3O^+]$. This relationship between acid strength of the catalyst and its catalytic ability can be expressed by the *Brønsted catalysis equation*[98]

$$\log k = \alpha \log K_a + C$$

where k is the rate constant for a reaction catalyzed by an acid of ionization constant K_a. According to this equation, when log k is plotted against log K_a for catalysis of a given reaction by a series of acids, a straight line should be obtained with slope α and intercept C. Although straight lines are obtained in many cases, this is not always the case. The relationship usually fails when acids of different types are compared. For example, it is much more likely to hold for a group of substituted phenols than for a collection of acids that contains both phenols and carboxylic acids. The Brønsted equation is another linear free-energy relationship (see p. 281).

Analogously, there are *general* and *specific* (S^- from an acidic solvent SH) *base-catalyzed reactions*. The Brønsted law for bases is

$$\log k = \beta \log K_b + C$$

The Brønsted equations relate a rate constant k to an equilibrium constant K_a. In Chapter 6 we saw that the Marcus equation also relates a rate term (in that case $\Delta G^{\ddagger}$) to an equilibrium term ΔG°. When the Marcus treatment is applied to proton transfers[99] between a carbon and an oxygen (or a nitrogen), the simplified[100] equation (p. 216)

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{\text{int}} + \tfrac{1}{2}\Delta G^\circ + \frac{(\Delta G^\circ)^2}{16\,\Delta G^{\ddagger}_{\text{int}}}$$

[97]For reviews, see Stewart, Ref. 1, pp. 251-305; Hammett, Ref. 81, pp. 315-345; Willi, in Bamford; Tipper, Ref. 72, pp. 1-95; Jones, Ref. 81, pp. 72-82; Bell, Ref. 1, pp. 159-193; Jencks *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969, pp. 163-242; Bender *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley: New York, 1971, pp. 19-144.

[98]For reviews, see Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982, pp. 167-179; Bell, in Chapman; Shorter *Correlation Analysis in Chemistry: Recent Advances*; Plenum Press: 1978, pp. 55-84; Kresge *Chem. Soc. Rev.* **1973,** *2*, 475-503.

[99]For applications of Marcus theory to proton transfers, see Marcus *J. Phys. Chem.* **1968,** *72*, 891; Kreevoy; Konasewich *Adv. Chem. Phys.* **1971,** *21*, 243; Kresge *Chem. Soc. Rev.* **1973,** *2*, 475-503.

[100]Omitting the work terms.

where

$$\Delta G^{\ddagger}_{\text{int}} = \tfrac{1}{2}\,(\Delta G^{\ddagger}_{\text{O,O}} + \Delta G^{\ddagger}_{\text{C,C}})$$

can be further simplified: Because proton transfers between oxygen and oxygen (or nitrogen and nitrogen) are much faster than those between carbon and carbon, $\Delta G^{\ddagger}_{\text{O,O}}$ is much smaller than $\Delta G^{\ddagger}_{\text{C,C}}$ and we can write[101]

$$\Delta G^{\ddagger} = \tfrac{1}{2}\,\Delta G^{\ddagger}_{\text{C,C}} + \tfrac{1}{2}\,\Delta G^{\circ} + \frac{(\Delta G^{\circ})^2}{8\,\Delta G^{\ddagger}_{\text{C,C}}}$$

Thus, if the carbon part of the reaction is kept constant and only the A of HA is changed (where A is an oxygen or nitrogen moiety), then $\Delta G^{\ddagger}$ is dependent only on ΔG°. Differentiation of this equation yields the Brønsted α:

$$\frac{d\Delta G^{\ddagger}}{d\Delta G^{\circ}} = \alpha = \tfrac{1}{2}\left(1 + \frac{\Delta G^{\circ}}{2\,\Delta G^{\ddagger}_{\text{C,C}}}\right)$$

The Brønsted law is therefore a special case of the Marcus equation.

A knowledge of whether a reaction is subject to general or specific acid catalysis supplies information about the mechanism. For any acid-catalyzed reaction we can write

Step 1 $$\mathbf{A} \overset{\text{SH}^+}{\rightleftharpoons} \mathbf{AH^+}$$

Step 2 $$\mathbf{AH^+} \longrightarrow \text{products}$$

If the reaction is catalyzed only by the specific acid SH^+, it means that step 1 is rapid and step 2 is rate-controlling, since an equilibrium has been rapidly established between A and the strongest acid present in the solution, namely, SH^+ (since this is the strongest acid that can be present in S). On the other hand, if step 2 is faster, there is no time to establish equilibrium and the rate-determining step must be step 1. This step is affected by all the acids present, and the rate reflects the sum of the effects of each acid (general acid catalysis). General acid catalysis is also observed if the slow step is the reaction of a hydrogen-bond complex A···HB, since each complex reacts with a base at a different rate. A comparable discussion can be used for general and specific base catalysis.[102] Further information can be obtained from the values α and β in the Brønsted catalysis equations, since these are approximate measures of the extent of proton transfer in the transition state. In most cases values of α and β are between 1 and 0. A value of α or β near 0 is generally taken to mean that the transition state resembles the reactants; i.e., the proton has been transferred very little when the transition state has been reached. A value of α or β near 1 is taken to mean the opposite; i.e., in the transition state the proton has been almost completely transferred. However, cases are known in which these generalizations are not followed,[103] and their theoretical basis has been challenged.[104] In general, the proton in the transition state lies closer to the weaker base.

[101]Albery *Annu. Rev. Phys. Chem.* **1980,** *31*, 227-263, p. 244.

[102]For discussions of when to expect general or specific acid or base catalysis, see Jencks *Acc. Chem. Res.* **1976,** *9*, 425-432; Stewart; Srinivasan *Acc. Chem. Res.* **1978,** *11*, 271-277; Guthrie *J. Am. Chem. Soc.* **1980,** *102*, 5286.

[103]See, for example, Bordwell; Boyle *J. Am. Chem. Soc.* **1972,** *94*, 3907; Davies *J. Chem. Soc., Perkin Trans. 2* **1974,** 1018; Agmon *J. Am. Chem. Soc.* **1980,** *102*, 2164; Murray; Jencks *J. Am. Chem. Soc.* **1988,** *110*, 7561.

[104]Pross; Shaik *New J. Chem.* **1989,** *13*, 427; Lewis, *J. Phys. Org. Chem.* **1990,** *3*, 1.

where

$$\Delta G^{\ddagger}_{\text{int}} = \tfrac{1}{2}(\Delta G^{\ddagger}_{\text{O,O}} + \Delta G^{\ddagger}_{\text{C,C}})$$

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[103]See, for example, Bordwell; Boyle *J. Am. Chem. Soc.* **1972,** *94*, 3907; Davies *J. Chem. Soc., Perkin Trans. 2* **1974,** 1018; Agmon *J. Am. Chem. Soc.* **1980,** *102*, 2164; Murray; Jencks *J. Am. Chem. Soc.* **1988,** *110*, 7561.
[104]Pross; Shaik *New J. Chem.* **1989,** *13*, 427; Lewis, *J. Phys. Org. Chem.* **1990,** *3*, 1.

Lewis Acids and Bases. Hard and Soft Acids and Bases

At about the same time that Brønsted proposed his acid–base theory, Lewis put forth a broader theory. A base in the Lewis theory is the same as in the Brønsted one, namely, a compound with an available pair of electrons, either unshared or in a π orbital. A *Lewis acid*, however, is any species with a vacant orbital.[105] In a Lewis acid–base reaction the unshared pair of the base forms a covalent bond with the vacant orbital of the acid, as represented by the general equation

$$\mathbf{A} + \overline{\mathbf{B}} \longrightarrow \mathbf{A{-}B}$$

in which charges are not shown, since they may differ. A specific example is

$$\mathbf{BF_3} + \overline{\mathbf{N}}\mathbf{H_3} \longrightarrow \mathbf{F_3}\overset{\ominus}{\mathbf{B}}{-}\overset{\oplus}{\mathbf{N}}\mathbf{H_3}$$

In the Brønsted picture, the acid is a proton donor, but in the Lewis picture the proton itself is the acid since it has a vacant orbital. A Brønsted acid becomes, in the Lewis picture, the compound that gives up the actual acid. The advantage of the Lewis theory is that it correlates the behavior of many more processes. For example, $AlCl_3$ and BF_3 are Lewis acids because they have only six electrons in the outer shell and have room for eight. $SnCl_4$ and SO_3 have eight, but their central elements, not being in the first row of the periodic table, have room for ten or twelve. Other Lewis acids are simple cations, like Ag^+. The simple reaction $A + \overline{B} \rightarrow A{-}B$ is not very common in organic chemistry, but the scope of the Lewis picture is much larger because reactions of the types

$$\mathbf{A^1 + A^2{-}B \longrightarrow A^1{-}B + A^2}$$

$$\mathbf{B^1 + A{-}B^2 \longrightarrow A{-}B^1 + B^2}$$

$$\mathbf{A^1{-}B^1 + A^2{-}B^2 \longrightarrow A^1{-}B^2 + A^2{-}B^1}$$

which are very common in organic chemistry, are also Lewis acid–base reactions. In fact, all reactions in which a covalent bond is formed through one species contributing a filled and the other a vacant orbital may be regarded as Lewis acid–base reactions.

When a Lewis acid combines with a base to give a negative ion in which the central atom has a higher-than-normal valence, the resulting salt is called an *ate complex*.[106] Examples are

$$\mathbf{Me_3B + LiMe \longrightarrow \underset{\text{Ate complex}}{Me_4B^-\ Li^+}}$$

$$\mathbf{Ph_5Sb + LiPh \longrightarrow \underset{\text{Ate complex}}{Ph_6Sb^-\ Li^+}}$$

Ate complexes are analogous to the onium salts formed when a Lewis base expands its valence, e.g.,

$$\mathbf{Me_3N + MeI \longrightarrow \underset{\text{Onium salt}}{Me_4N^+\ I^-}}$$

[105] For a monograph on Lewis acid–base theory, see Jensen *The Lewis Acid–Base Concept*; Wiley: New York, 1980. For a discussion of the definitions of Lewis acid and base, see Jensen *Chem. Rev.* **1978,** *78*, 1-22.

[106] For a review of ate complexes, see Wittig *Q. Rev., Chem. Soc.* **1966,** *20*, 191-210.

Far fewer quantitative measurements have been made of Lewis acid strength compared to that of Brønsted acids.[107] A simple table of Lewis acidities based on some quantitative measurement (such as that given for Brønsted acids in Table 8.1) is not feasible because Lewis acidity depends on the nature of the base. Qualitatively, the following approximate sequence of acidity of Lewis acids of the type MX_n has been suggested, where X is a halogen atom or an inorganic radical: $BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > SnX_4 > AsX_5 > ZnX_2 > HgX_2$.

The facility with which an acid–base reaction takes place depends of course on the strengths of the acid and the base. But it also depends on quite another quality, called the *hardness* or *softness* of the acid or base.[108] Hard and soft acids and bases have these characteristics:

Soft bases. The donor atoms are of low electronegativity and high polarizability and are easy to oxidize. They hold their valence electrons loosely.

Hard bases. The donor atoms are of high electronegativity and low polarizability and are hard to oxidize. They hold their valence electrons tightly.

Soft acids. The acceptor atoms are large, have low positive charge, and contain unshared pairs of electrons (*p* or *d*) in their valence shells. They have high polarizability and low electronegativity.

Hard acids. The acceptor atoms are small, have high positive charge, and do not contain unshared pairs in their valence shells. They have low polarizability and high electronegativity.

A qualitative listing of the hardness of some acids and bases is given in Table 8.2.[109] The treatment has also been made quantitative,[110] with the following operational definition:

$$\eta = \frac{I - A}{2}$$

In this equation η, the *absolute hardness*, is half the difference between I, the ionization potential, and A, the electron affinity. The softness, σ, is the reciprocal of η. Values of η for some molecules and ions are given in Table 8.3.[111] Note that the proton, which is involved in all Brønsted acid–base reactions, is the hardest acid listed, with $\eta = \infty$ (it has no ionization potential). The above equation cannot be applied to anions, because electron affinities cannot be measured for them. Instead, the assumption is made that η for an anion X^- is the same as that for the radical X•.[112] Other methods are also needed to apply the treatment to polyatomic cations.[112]

[107]For reviews of the quantitative aspects of Lewis acidity, see Satchell; Satchell *Q. Rev., Chem. Soc.* **1971,** *25*, 171-199, *Chem. Rev.* **1969,** *69*, 251-278. See also Maria; Gal *J. Phys. Chem.* **1985,** *89*, 1296; Larson; McMahon *J. Am. Chem. Soc.* **1985,** *107*, 766; Larson; Szulejko; McMahon *J. Am. Chem. Soc.* **1988,** *110*, 7604; Sandström; Persson; Persson *Acta Chem. Scand.* **1990,** *44*, 653; Laszlo; Teston-Henry *Tetrahedron Lett.* **1991,** *32*, 3837.

[108]Pearson *J. Am. Chem. Soc.* **1963,** *85*, 3533, *Science* **1966,** *151*, 172; Pearson; Songstad *J. Am. Chem. Soc.* **1967,** *89*, 1827. For a monograph on the concept, see Ho *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977. For reviews, see Pearson, *J. Chem. Educ.* **1987,** *64*, 561-567; Ho *Tetrahedron* **1985,** *41*, 1-86, *J. Chem. Educ.* **1978,** 55, 355-360, *Chem. Rev.* **1975,** *75*, 1-20; Pearson, in Chapman; Shorter *Advances in Linear Free-Energy Relationships*; Plenum Press: New York, 1972, pp. 281-319; Pearson *Surv. Prog. Chem.* **1969,** *5*, 1-52 [portions of this article slightly modified also appear in Pearson *J. Chem. Educ.* **1968,** 45, 581-587, 643-648]; Garnovskii; Osipov; Bulgarevich *Russ. Chem. Rev.* **1972,** *41*, 341-359; Seyden-Penne *Bull. Soc. Chim. Fr.* **1968,** 3871-3878. For a collection of papers, see Pearson *Hard and Soft Acids and Bases*; Dowden, Hutchinson, and Ross: Stroudsberg, PA, 1973.

[109]Taken from larger listings in Pearson, Ref. 108.

[110]Parr; Pearson *J. Am. Chem. Soc.* **1983,** *105*, 7512; Pearson *Inorg. Chem.* **1988,** *27*, 734. *J. Org. Chem.* **1989,** *54*, 1423. See also Orsky; Whitehead *Can. J. Chem.* **1987,** *65*, 1970.

[111]Note that there is not always a strict correlation between the values in Table 8.3 and the categories of Table 8.2.

[112]Pearson *J. Am. Chem. Soc.* **1988,** *110*, 7684.

TABLE 8.2 Hard and soft acids and bases[109]

Hard bases	Soft bases	Borderline bases
H_2O OH^- F^-	R_2S RSH RS^-	$ArNH_2$ C_5H_5N
AcO^- SO_4^{2-} Cl^-	I^- R_3P $(RO)_3P$	N_3^- Br^-
CO_3^{2-} NO_3^- ROH	CN^- RCN CO	NO_2^-
RO^- R_2O NH_3	C_2H_4 C_6H_6	
RNH_2	H^- R^-	
Hard acids	**Soft acids**	**Borderline acids**
H^+ Li^+ Na^+	Cu^+ Ag^+ Pd^{2+}	Fe^{2+} Co^{2+} Cu^{2+}
K^+ Mg^{2+} Ca^{2+}	Pt^{2+} Hg^{2+} BH_3	Zn^{2+} Sn^{2+} Sb^{3+}
Al^{3+} Cr^{2+} Fe^{3+}	$GaCl_3$ I_2 Br_2	Bi^{3+} BMe_3 SO_2
BF_3 $B(OR)_3$ $AlMe_3$	CH_2 carbenes	R_3C^+ NO^+ GaH_3
$AlCl_3$ AlH_3 SO_3		$C_6H_5^+$
RCO^+ CO_2		
HX (hydrogen-bonding molecules)		

TABLE 8.3 Some absolute hardness values in electron volts[110]

Cations		Molecules		Anions[b]	
Ion	η	Compound	η	Ion	η
H^+	∞	HF	11.0	F^-	7.0
Al^{3+}	45.8	CH_4	10.3	H^-	6.4
Li^+	35.1	BF_3	9.7	OH^-	5.7
Mg^{2+}	32.6	H_2O	9.5	NH_2^-	5.3
Na^+	21.1	NH_3	8.2	CN^-	5.1
Ca^{2+}	19.5	HCN	8.0	CH_3^-	4.9
K^+	13.6	$(CH_3)_2O$	8.0	Cl^-	4.7
Zn^{2+}	10.9	CO	7.9	$CH_3CH_2^-$	4.4
Cr^{3+}	9.1	C_2H_2	7.0	Br^-	4.2
Cu^{2+}	8.3	$(CH_3)_3N$	6.3	$C_6H_5^-$	4.1
Pt^{2+}	8.0	H_2S	6.2	SH^-	4.1
Sn^{2+}	7.9	C_2H_4	6.2	$(CH_3)_2CH^-$	4.0
Hg^{2+}	7.7	$(CH_3)_2S$	6.0	I^-	3.7
Fe^{2+}	7.2	$(CH_3)_3P$	5.9	$(CH_3)_3C^-$	3.6
Pd^{2+}	6.8	CH_3COCH_3	5.6		
Cu^+	6.3	C_6H_6	5.3		
		HI	5.3		
		C_5H_5N	5.0		
		C_6H_5OH	4.8		
		CH_2[a]	4.7		
		C_6H_5SH	4.6		
		Cl_2	4.6		
		$C_6H_5NH_2$	4.4		
		Br_2	4.0		
		I_2	3.4		

[a]For singlet state.
[b]The same as for the corresponding radical.

Once acids and bases have been classified as hard or soft, a simple rule can be given: *hard acids prefer to bond to hard bases, and soft acids prefer to bond to soft bases* (*the HSAB principle*).[112a] The rule has nothing to do with acid or base *strength* but merely says that the product A—B will have extra stability if both A and B are hard or if both are soft. Another rule is that a soft Lewis acid and a soft Lewis base tend to form a covalent bond, while a hard acid and a hard base tend to bond ionically.

One application of the first rule given above is found in complexes between alkenes or aromatic compounds and metal ions (p. 80). Alkenes and aromatic rings are soft bases and should prefer to complex with soft acids. Thus, Ag^+, Pt^{2+}, and Hg^{2+} complexes are common, but complexes of Na^+, Mg^{2+}, or Al^{3+} are rare. Chromium complexes are also common, but in such complexes the chromium is in a low or zero oxidation state (which softens it) or attached to other soft ligands. In another application, we may look at this reaction:

$$CH_3-\underset{\underset{O}{\|}}{C}-SR' + OR^- \rightleftharpoons CH_3-\underset{\underset{O}{\|}}{C}-OR + SR'^-$$

The HSAB principle predicts that the equilibrium should lie to the right, because the hard acid CH_3CO^+ should have a greater affinity for the hard base RO^- than for the soft base RS^-. Indeed, thiol esters are easily cleaved by OR^- or hydrolyzed by dilute base (OH^- is also a hard base).[113] Another application of the rule is discussed on p. 349.[114]

The Effects of Structure on the Strengths of Acids and Bases[115]

The structure of a molecule can affect its acidity or basicity in a number of ways. Unfortunately, in most molecules two or more of these effects (as well as solvent effects) are operating, and it is usually very difficult or impossible to say how much each effect contributes to the acid or base strength.[116] Small differences in acidity or basicity between similar molecules are particularly difficult to interpret. It is well to be cautious when attributing them to any particular effect.

1. *Field effects.* These were discussed on p. 17. As an example of the influence of field effects on acidity, we may compare the acidity of acetic acid and nitroacetic acid:

$$H-CH_2-\underset{\underset{O}{\|}}{C}-O-H \qquad O_2N-CH_2-\underset{\underset{O}{\|}}{C}-O-H$$

$$pK_a = 4.76 \qquad\qquad pK_a = 1.68$$

[112a]For proofs of this principle, see Chattaraj; Lee; Parr *J. Am. Chem. Soc.* **1991,** *113,* 1855.

[113]Wolman, in Patai *The Chemistry of the Thiol Group*, pt. 2; Wiley: New York, 1974, p. 677; Maskill *The Physical Basis of Organic Chemistry*; Oxford University Press: Oxford, 1985, p. 159.

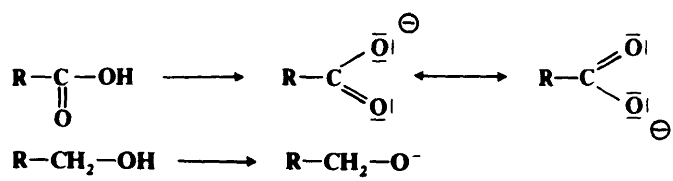
[114]See also Bochkov *J. Org. Chem. USSR* **1986,** *22,* 1830, 1837.

[115]For a monograph, see Hine *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975. For reviews, see Taft *Prog. Phys. Org. Chem.* **1983,** *14,* 247-350; Petrov *Russ. Chem. Rev.* **1983,** *52,* 1144-1155 (NH acids); Bell, Ref. 1, pp. 86-110; Barlin; Perrin, in Bentley; Kirby *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (vol. 4 of Weissberger *Techniques of Chemistry*), pt. 1; Wiley: New York, 1972, pp. 611-676. For discussions, see Bolton; Hepler *Q. Rev., Chem. Soc.* **1971,** *25,* 521-532; Barlin; Perrin *Q. Rev., Chem. Soc.* **1966,** *20,* 75-101; Thirot *Bull. Soc. Chim. Fr.* **1967,** 3559; Liler, Ref. 10, pp. 59-144. For a monograph on methods of estimating p*K* values by analogy, extrapolation, etc., see Perrin; Dempsey; Serjeant *pK_a Prediction for Organic Acids and Bases*; Chapman and Hall: New York, 1981.

[116]The varying degrees by which the different factors that affect gas-phase acidities of 25 acids has been calculated: Taft; Koppel; Topsom; Anvia *J. Am. Chem. Soc.* **1990,** *112,* 2047.

The only difference in the structure of these molecules is the substitution of NO_2 for H. Since NO_2 is a strongly electron-withdrawing group, it withdraws electron density from the negatively charged COO^- group in the anion of nitroacetic acid (compared with the anion of acetic acid) and, as the pK_a values indicate, nitroacetic acid is about 1000 times stronger than acetic acid.[117] Any effect that results in electron withdrawal from a negatively charged center is a stabilizing effect because it spreads the charge. Thus, $-I$ groups increase the acidity of uncharged acids such as acetic because they spread the negative charge of the anion. However, $-I$ groups also increase the acidity of any acid, no matter what the charge. For example, if the acid has a charge of +1 (and its conjugate base is therefore uncharged), a $-I$ group destabilizes the positive center (by increasing and concentrating the positive charge) of the acid, a destabilization that will be relieved when the proton is lost. In general we may say that *groups that withdraw electrons by the field effect increase acidity and decrease basicity, while electron-donating groups act in the opposite direction.* Another example is the molecule $(C_6F_5)_3CH$, which has three strongly electron-withdrawing C_6F_5 groups and a pK_a of 16,[118] compared with Ph_3CH, with a pK_a of 31.5 (Table 8.1), an acidity enhancement of about 10^{15}. Table 8.4 shows pK_a values for some acids. An approximate idea of field effects can be obtained from this table. In the case of the chlorobutyric acids note how the effect decreases with distance. It must be remembered, however, that field effects are not the sole cause of the acidity differences noted and that in fact solvation effects may be more important in many cases (see pp. 269-272).[119]

2. *Resonance effects.* Resonance that stabilizes a base but not its conjugate acid results in the acid having a higher acidity than otherwise expected and vice versa. An example is found in the higher acidity of carboxylic acids compared with primary alcohols.



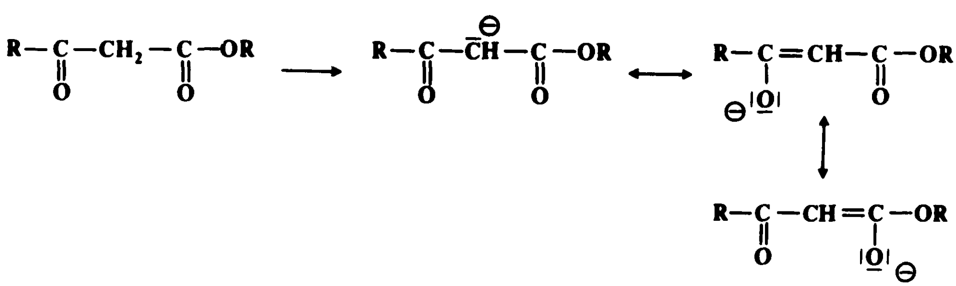
The $RCOO^-$ ion is stabilized by resonance not available to the RCH_2O^- ion (or to RCOOH).[120] Note that the $RCOO^-$ is stabilized not only by the fact that there are two equivalent canonical forms but also by the fact that the negative charge is spread over both oxygen atoms and is therefore less concentrated than in RCH_2O^-. The same effect is found in other compounds containing a C=O or C≡N group. Thus amides $RCONH_2$ are more acidic than amines RCH_2NH_2; esters RCH_2COOR' than ethers RCH_2CH_2OR'; and ketones RCH_2COR' than alkanes RCH_2CH_2R' (Table 8.1). The effect is enhanced when two carbonyl groups are attached to the same carbon (because of additional resonance and spreading

[117]For a review of the enhancement of acidity by NO_2, see Lewis, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 2; Wiley: New York, 1982, pp. 715-729.
[118]Filler; Wang *Chem. Commun.* **1968,** 287.
[119]For discussions, see Edward *J. Chem. Educ.* **1982,** *59,* 354; Schwartz *J. Chem. Educ.* **1981,** *58,* 778.
[120]It has been contended that resonance delocalization plays only a minor role in the increased strength of carboxylic acids compared to alcohols, and the ". . . higher acidity of acids arises principally because the electrostatic potential of the acidic hydrogens is more positive in the neutral acid molecule . . .": Siggel; Thomas *J. Am. Chem. Soc.* **1986,** *108,* 4360; Siggel; Streitwieser; Thomas *J. Am. Chem. Soc.* **1988,** *110,* 8022; Thomas; Carroll; Siggel *J. Org. Chem.* **1988,** *53,* 1812. For contrary views, see Exner *J. Org. Chem.* **1988,** *53,* 1810; Dewar; Krull *J. Chem. Soc., Chem. Commun.* **1990,** 333; Perrin *J. Am. Chem. Soc.* **1991,** *113,* 2865. See also Godfrey *Tetrahedron Lett.* **1990,** *31,* 5181.

TABLE 8.4 p*K* values for some acids[39]

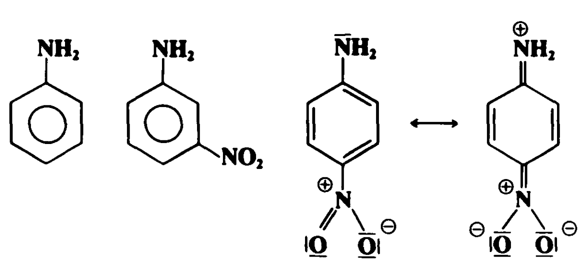
Acid	p*K*	Acid	p*K*
HCOOH	3.77	$ClCH_2COOH$	2.86
CH_3COOH	4.76	$Cl_2CHCOOH$	1.29
CH_3CH_2COOH	4.88	Cl_3CCOOH	0.65
$CH_3(CH_2)_nCOOH$ (n = 2 to 7)	4.82–4.95	O_2NCH_2COOH	1.68
$(CH_3)_2CHCOOH$	4.86	$(CH_3)_3\overset{\oplus}{N}CH_2COOH$	1.83
$(CH_3)_3CCOOH$	5.05	$HOOCCH_2COOH$	2.83
		$PhCH_2COOH$	4.31
FCH_2COOH	2.66	$\overset{\ominus}{O}OCCH_2COOH$	5.69
$ClCH_2COOH$	2.86		
$BrCH_2COOH$	2.86		
ICH_2COOH	3.12	$\overset{\ominus}{O}_3SCH_2COOH$	4.05
		$HOCH_2COOH$	3.83
$ClCH_2CH_2CH_2COOH$	4.52	$H_2C{=}CHCH_2COOH$	4.35
$CH_3CHClCH_2COOH$	4.06		
$CH_3CH_2CHClCOOH$	2.84		

of charge); for example, β-keto esters are more acidic than simple ketones or carboxylic esters (Table 8.1). Extreme examples of this effect are found in the molecules tricyano-



methane $(NC)_3CH$, with a pK_a of −5, and 2-(dicyanomethylene)-1,1,3,3-tetracyanopropene $(NC)_2C{=}C[CH(CN)_2]_2$, whose first pK_a is below −8.5 and whose second pK_a is −2.5.

Resonance effects are also important in aromatic amines. *m*-Nitroaniline is a weaker base than aniline, a fact that can be accounted for by the −*I* effect of the nitro group. But



pK_a of conjugate[122] acid 4.60 2.47 1.11

A

p-nitroaniline is weaker still, though the $-I$ effect should be less because of the greater distance. We can explain this result by taking into account the canonical form **A**. Because **A** contributes to the resonance hybrid,[121] the electron density of the unshared pair is lower in *p*-nitroaniline than in *m*-nitroaniline, where a canonical form such as **A** is impossible. The basicity is lower in the para compound for two reasons, both caused by the same effect: (1) the unshared pair is less available for attack by a proton, and (2) when the conjugate acid is formed, the resonance stabilization afforded by **A** is no longer available because the previously unshared pair is now being shared by the proton. The acidity of phenols is affected by substituents in a similar manner.

In general, resonance effects lead to the same result as field effects. That is, here too, electron-withdrawing groups increase acidity and decrease basicity, and electron-donating groups act in the opposite manner. As a result of both resonance and field effects, charge dispersal leads to greater stability.

3. *Periodic table correlations.* When comparing Brønsted acids and bases that differ in the position of an element in the periodic table:

a. Acidity increases and basicity decreases in going from left to right across a row of the periodic table. Thus acidity increases in the order $CH_4 < NH_3 < H_2O < HF$, and basicity decreases in the order $CH_3^- > NH_2^- > OH^- > F^-$. This behavior can be explained by the increase in electronegativity upon going from left to right across the table. It is this effect that is responsible for the great differences in acidity between carboxylic acids, amides, and ketones: $RCOOH \gg RCONH_2 \gg RCOCH_3$.

b. Acidity increases and basicity decreases in going down a column of the periodic table, despite the decrease in electronegativity. Thus acidity increases in the order $HF < HCl < HBr < HI$ and $H_2O < H_2S$, and basicity decreases in the order $NH_3 > PH_3 > AsH_3$. This behavior is related to the size of the species involved. Thus, for example, F^-, which is much smaller than I^-, attracts a proton much more readily because its negative charge occupies a smaller volume and is therefore more concentrated (note that F^- is also much harder than I^- and is thus more attracted to the hard proton; see p. 263). This rule does not always hold for positively charged acids. Thus, although the order of acidity for the group 16 hydrides is $H_2O < H_2S < H_2Se$, the acidity order for the positively charged ions is $H_3O^+ > H_3S^+ > H_3Se^+$.[123]

Lewis acidity is also affected by periodic table considerations. In comparing acid strengths of Lewis acids of the form MX_n:[107]

c. Acids that require only one electron pair to complete an outer shell are stronger than those that require two. Thus $GaCl_3$ is stronger than $ZnCl_2$. This results from the relatively smaller energy gain in adding an electron pair that does not complete an outer shell and from the buildup of negative charge if two pairs come in.

d. Other things being equal, the acidity of MX_n decreases in going down the periodic table because as the size of the molecule increases, the attraction between the positive nucleus and the incoming electron pair is weaker. Thus BCl_3 is a stronger acid than $AlCl_3$.[124]

4. *Statistical effects.* In a symmetrical diprotic acid, the first dissociation constant is twice as large as expected since there are two equivalent ionizable hydrogens, while the second constant is only half as large as expected because the conjugate base can accept a proton at two equivalent sites. So K_1/K_2 should be 4, and approximately this value is found

[121]See, however, Lipkowitz *J. Am. Chem. Soc.* **1982**, *104*, 2647; Krygowski; Maurin *J. Chem. Soc., Perkin Trans. 2* **1989**, 695.

[122]Smith, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 161-204.

[123]Taft, Ref. 115, pp. 250-254.

[124]Note that Lewis acidity *decreases*, whereas Brønsted acidity *increases*, going down the table. There is no contradiction here when we remember that in the Lewis picture the actual acid in all Brønsted acids is the same, namely, the proton. In comparing, say, HI and HF, we are not comparing different Lewis acids but only how easily F^- and I^- give up the proton.

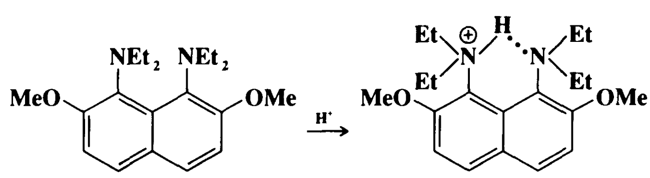
for dicarboxylic acids where the two groups are sufficiently far apart in the molecule that they do not influence each other. A similar argument holds for molecules with two equivalent basic groups.[125]

5. *Hydrogen bonding.* Internal hydrogen bonding can greatly influence acid or base strength. For example, the p*K* for *o*-hydroxybenzoic acid is 2.98, while the value for the para isomer is 4.58. Internal hydrogen bonding between the OH and COO^- groups of the conjugate base of the ortho isomer stabilizes it and results in an increased acidity.

6. *Steric effects.* The proton itself is so small that direct steric hindrance is seldom encountered in proton transfers. Steric effects are much more common in Lewis acid–base reactions in which larger acids are used. Spectacular changes in the order of base strength have been demonstrated when the size of the acid was changed. Table 8.5 shows the order of base strength of simple amines when compared against acids of various size.[126] It can be seen that the usual order of basicity of amines (when the proton is the reference acid) can be completely inverted by using a large enough acid. The strain caused by formation of a covalent bond when the two atoms involved each have three large groups is called *face strain* or *F strain*.

Steric effects can indirectly affect acidity or basicity by affecting the resonance (see p. 37). For example, *o*-*t*-butylbenzoic acid is about 10 times as strong as the para isomer, because the carboxyl group is forced out of the plane by the *t*-butyl group. Indeed, virtually all ortho benzoic acids are stronger than the corresponding para isomers, regardless of whether the group on the ring is electron-donating or electron-withdrawing.

Steric effects can also be caused by other types of strain. 1,8-Bis(diethylamino)-2,7-dimethoxynaphthalene (**1**) is an extremely strong base for a tertiary amine (pK_a of the



1 **2**

conjugate acid = 16.3; compare N,N-dimethylaniline, pK_a = 5.1), but proton transfers to

TABLE 8.5 Bases listed in increasing order of base strength when compared with certain reference acids

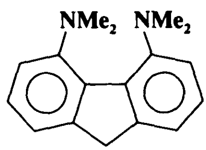
Increasing order of base strength[a]	Reference acid: H^+ or BMe_3	BMe_3	$B(CMe_3)_3$	
↓	NH_3	Et_3N	Me_3N	Et_3N
	Me_3N	NH_3	Me_2NH	Et_2NH
	$MeNH_2$	Et_2NH	NH_3	$EtNH_2$
	Me_2NH	$EtNH_2$	$MeNH_2$	NH_3

[a]The order of basicity (when the reference acids were boranes) was determined by the measurement of dissociation pressures.

[125]The effect discussed here is an example of a symmetry factor. For an extended discussion, see Eberson, in Patai *The Chemistry of Carboxylic Acids and Esters*; Wiley: New York, 1969, pp. 211-293.

[126]Brown *J. Am. Chem. Soc.* **1945,** *67*, 378, 1452, *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972, pp. 53-64. See also Brown; Krishnamurthy; Hubbard *J. Am. Chem. Soc.* **1978,** *100*, 3343.

and from the nitrogen are exceptionally slow; slow enough to be followed by a uv spectrophotometer.[127] **1** is severely strained because the two nitrogen lone pairs are forced to be near each other.[128] Protonation relieves the strain: one lone pair is now connected to a hydrogen, which forms a hydrogen bond to the other lone pair (shown in **2**). The same effects are found in 4,5-bis(dimethylamino)fluorene (**3**)[129] and 4,5-bis(dimethylamino)-



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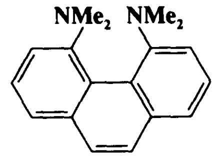
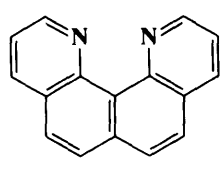
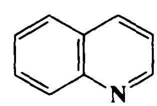


4

phenanthrene (**4**).[130] Compounds such as **1, 3,** and **4** are known as *proton sponges*.[131] Another type of proton sponge is quino[7,8-*h*]quinoline (**5**).[132] Protonation of this compound also gives a stable monoprotonated ion similar to **2**, but the steric hindrance found in **1, 3,** and



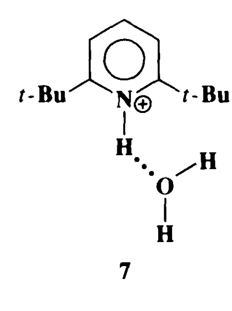
5



6

4 is absent. Therefore **5** is a much stronger base than quinoline (**6**) (pK_a values of the conjugate acids are 12.8 for **5** and 4.9 for **6**), but proton transfers are not abnormally slow.

Another type of steric effect is the result of an entropy effect. The compound 2,6-di-*t*-butylpyridine is a weaker base than either pyridine or 2,6-dimethylpyridine.[133] The reason is that the conjugate acid (**7**) is less stable than the conjugate acids of non-sterically



7

[127]Alder; Goode; Miller; Hibbert; Hunte; Robbins *J. Chem. Soc., Chem. Commun.* **1978,** 89; Hibbert; Hunte *J. Chem. Soc., Perkin Trans. 2* **1983,** 1895; Barnett; Hibbert *J. Am. Chem. Soc.* **1984,** *106*, 2080; Hibbert; Simpson *J. Chem. Soc., Perkin Trans. 2* **1987,** 243, 613.

[128]For a review of the effect of strain on amine basicities, see Alder *Chem. Rev.* **1989,** *89*, 1215-1223.

[129]Staab; Saupe; Krieger *Angew. Chem. Int. Ed. Engl.* **1983,** *22*, 731 [*Angew. Chem.* *95*, 748].

[130]Saupe; Krieger; Staab *Angew. Chem. Int. Ed. Engl.* **1986,** *25*, 451 [*Angew. Chem.* *98*, 460].

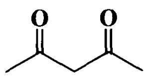
[131]For a review, see Staab; Saupe *Angew. Chem. Int. Ed. Engl.* **1988,** *27*, 865-879 [*Angew. Chem.* 895-909].

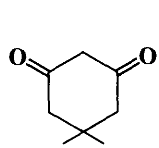
[132]Zirnstein; Staab *Angew. Chem. Int. Ed. Engl.* **1987,** *26*, 460 [*Angew. Chem.* *99*, 460]; Krieger; Newsom; Zirnstein; Staab *Angew. Chem. Int. Ed. Engl.* **1989,** *28*, 84 [*Angew. Chem.* *101*, 72]. See also Schwesinger; Missfeldt; Peters; Schnering *Angew. Chem.Int. Ed. Engl.* **1987,** *26*, 1165 [*Angew. Chem.* *99*, 1210]; Alder; Eastment; Hext; Moss; Orpen; White *J. Chem. Soc., Chem. Commun.* **1988,** 1528; Staab; Zirnstein; Krieger *Angew. Chem. Int. Ed. Engl.* **1989,** *28*, 86 [*Angew. Chem.* *101*, 73].

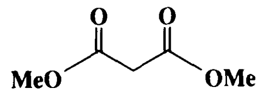
[133]Brown; Kanner *J. Am. Chem. Soc.* **1953,** *75*, 3865; **1966,** *88*, 986.

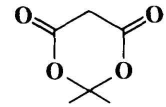
hindered pyridines. In all cases the conjugate acids are hydrogen-bonded to a water molecule, but in the case of **7** the bulky *t*-butyl groups restrict rotations in the water molecule, lowering the entropy.[134]

The conformation of a molecule can also affect its acidity. The following pK_a values were determined for these compounds:[135]



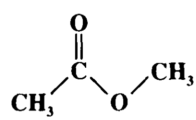




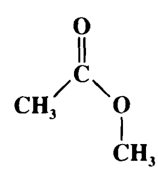


	8	9	10	11
pK_a	13.3	11.2	15.9	7.3

Since ketones are stronger acids than carboxylic esters (Table 8.1), we are not surprised that **8** is a stronger acid than **10.** But cyclization of **8** to **9** increases the acidity by only 2.1 pK units while cyclization of **10** to **11** increases it by 8.6 units. Indeed, it has long been known that **11** (called Meldrum's acid) is an unusually strong acid for a 1,3-diester. In order to account for this very large cyclization effect, molecular orbital calculations were carried out two conformations of methyl acetate and of its enolate ion by two groups.[136] Both found



syn



anti

that loss of a proton is easier by about 5 kcal/mol (21 kJ/mol) for the syn than for the anti conformer of the ester. In an acyclic molecule like **10** the preferred conformations are anti, but in Meldrum's acid **(11)** the conformation on both sides is constrained to be syn.

7. *Hybridization.* An *s* orbital has a lower energy than a *p* orbital. Therefore the energy of a hybrid orbital is lower the more *s* character it contains. It follows that a carbanion at an *sp* carbon is more stable than a corresponding carbanion at an sp^2 carbon. Thus $HC{\equiv}C^-$, which has more *s* character in its unshared pair than $CH_2{=}CH^-$ or $CH_3CH_2^-$ (*sp* vs. sp^2 vs. sp^3, respectively), is a much weaker base. This explains the relatively high acidity of acetylenes and HCN. Another example is that alcohol and ether oxygens, where the unshared pair is sp^3, are more strongly basic than carbonyl oxygens, where the unshared pair is sp^2 (Table 8.1).

The Effects of the Medium on Acid and Base Strength

Structural features are not the only factors that affect acidity or basicity. The same compound can have its acidity or basicity changed when the conditions are changed. The effect of

[134]Meot-Ner; Sieck *J. Am. Chem. Soc.* **1983,** *105*, 2956; Hopkins; Jahagirdar; Moulik; Aue; Webb; Davidson; Pedley *J. Am. Chem. Soc.* **1984,** *106*, 4341; Meot-Ner; Smith *J. Am. Chem. Soc.* **1991,** *113*, 862, and references cited in these papers. See also Benoit; Fréchette; Lefebvre *Can. J. Chem.* **1988,** *66*, 1159.

[135]Arnett; Harrelson *J. Am. Chem. Soc.* **1987,** *109*, 809.

[136]Wang; Houk *J. Am. Chem. Soc.* **1988,** *110*, 1870; Wiberg; Laidig *J. Am. Chem. Soc.* **1988,** *110*, 1872.

temperature (p. 253) has already been mentioned. More important is the effect of the solvent, which can exert considerable influence on acid and base strengths by differential solvation.[137] If a base is more solvated than its conjugate acid, its stability is increased relative to the conjugate acid. For example, Table 8.5 shows that toward the proton, where steric effects are absent, methylamine is a stronger base than ammonia and dimethylamine is stronger still.[138] These results are easily explainable if one assumes that methyl groups are electron-donating. However, trimethylamine, which should be even stronger, is a weaker base than dimethylamine or methylamine. This apparently anomalous behavior can be explained by differential hydration.[139] Thus, NH_4^+ is much better hydrated (by hydrogen bonding to the water solvent) than NH_3 because of its positive charge.[140] It has been estimated that this effect contributes about 11 p*K* units to the base strength of ammonia.[141] When methyl groups replace hydrogen, this difference in hydration decreases[142] until, for trimethylamine, it contributes only about 6 p*K* units to the base strength.[141] Thus two effects act in opposite directions, the field effect increasing the basicity as the number of methyl groups increases and the hydration effect decreasing it. When the effects are added, the strongest base is dimethylamine and the weakest is ammonia. If alkyl groups are electron-donating, one would expect that in the gas phase,[143] where the solvation effect does not exist, the basicity order of amines toward the proton should be $R_3N > R_2NH > RNH_2 > NH_3$, and this has indeed been confirmed, for R = Me as well as R = Et and Pr.[144] Aniline too, in the gas phase, is a stronger base than NH_3,[145] so its much lower basicity in aqueous solution (pK_a of $PhNH_3^+$ 4.60 compared with 9.24 for aqueous NH_4^+) is caused by similar solvation effects and not by resonance and field electron-withdrawing effects of a phenyl group. Similarly, pyridine[146] and pyrrole[147] are both much less basic than NH_3 in aqueous solution (pyrrole[148] is neutral in aqueous solution) but *more* basic in the gas phase. These examples in particular

[137]For reviews of the effects of solvent, see Epshtein; Iogansen *Russ. Chem. Rev.* **1990,** *59*, 134-151; Dyumaev; Korolev *Russ. Chem. Rev.* **1980,** *49*, 1021-1032. For a review of the effects of the solvent dimethyl sufoxide, see Taft; Bordwell *Acc. Chem. Res.* **1988,** *21*, 463-469.

[138]For a review of the basicity of amines, see Ref. 122.

[139]Trotman-Dickenson *J. Chem. Soc.* **1949,** 1293; Pearson *J. Am. Chem. Soc.* **1948,** *70*, 204; Pearson; Williams *J. Am. Chem. Soc.* **1954,** *76*, 258; Hall *J. Am. Chem. Soc.* **1957,** *79*, 5441; Arnett; Jones; Taagepera; Henderson; Beauchamp; Holtz; Taft *J. Am. Chem. Soc.* **1972,** *94*, 4724; Aue; Webb; Bowers *J. Am. Chem. Soc.* **1972,** *94*, 4726, **1976,** *98*, 311, 318; Mucci; Domain; Benoit *Can. J. Chem.* **1980,** *58*, 953. See also Drago; Cundari; Ferris *J. Org. Chem.* **1989,** *54*, 1042.

[140]For discussions of the solvation of ammonia and amines, see Jones; Arnett *Prog. Phys. Org. Chem.* **1974,** *11*, 263-420; Grunwald; Ralph *Acc. Chem. Res.* **1971,** *4*, 107-113.

[141]Condon *J. Am. Chem. Soc.* **1965,** *87*, 4481, 4485.

[142]For two reasons: (1) the alkyl groups are poorly solvated by the water molecules, and (2) the strength of the hydrogen bonds of the BH^+ ions decreases as the basicity of B increases: Lau; Kebarle *Can. J. Chem.* **1981,** *59*, 151.

[143]For reviews of acidities and basicities in the gas phase, see Liebman *Mol. Struct. Energ.* **1987,** *4*, 49-70; Dixon; Lias *Mol. Struct. Energ.* **1987,** *2*, 269-314; Bohme, in Patai, Ref. 117, pp. 731-762; Bartmess; McIver, in Bowers *Gas Phase Ion Chemistry*, vol. 2; Academic Press: New York, 1979, pp. 88-121; Kabachnik *Russ. Chem. Rev.* **1979,** *48*, 814-827; Kebarle *Annu. Rev. Phys. Chem.* **1977,** *28*, 445-476; Arnett *Acc. Chem. Res.* **1973,** *6*, 404-409. For a comprehensive table of gas-phase basicities, see Lias; Liebman; Levin *J. Phys. Chem. Ref. Data* **1984,** *13*, 695-808. See also the tables of gas-phase acidities and basicities in Meot-Ner; Kafafi *J. Am. Chem. Soc.* **1988,** *110*, 6297; Headley *J. Am. Chem. Soc.* **1987,** *109*, 2347; McMahon; Kebarle *J. Am. Chem. Soc.* **1985,** *107*, 2612, **1977,** *99*, 2222, 3399; Wolf; Staley; Koppel; Taagepera; McIver; Beauchamp; Taft *J. Am. Chem. Soc.* **1977,** *99*, 5417; Cumming; Kebarle *J. Am. Chem. Soc.* **1977,** *99*, 5818, **1978,** *100*, 1835, *Can. J. Chem.* **1978,** *56*, 1; Bartmess; Scott; McIver *J. Am. Chem. Soc.* **1979,** *101*, 6046; Fujio; McIver; Taft *J. Am. Chem. Soc.* **1981,** *103*, 4017; Lau; Nishizawa; Tse; Brown; Kebarle *J. Am. Chem. Soc.* **1981,** *103*, 6291.

[144]Munson *J. Am. Chem. Soc.* **1965,** *87*, 2332; Brauman; Riveros; Blair *J. Am. Chem. Soc.* **1971,** *93*, 3914; Briggs; Yamdagni; Kebarle *J. Am. Chem. Soc.* **1972,** *94*, 5128; Aue; Webb; Bowers, Ref. 139.

[145]Briggs; Yamdagni; Kebarle, Ref. 144, Dzidic *J. Am. Chem. Soc.* **1972,** *94*, 8333; Ikuta; Kebarle *Can. J. Chem.* **1983,** *61*, 97.

[146]Taagepera; Henderson; Brownlee; Beauchamp; Holtz; Taft *J. Am. Chem. Soc.* **1972,** *94*, 1369; Taft; Taagepera; Summerhays; Mitsky *J. Am. Chem. Soc.* **1973,** *95*, 3811; Briggs; Yamdagni; Kebarle, Ref. 144.

[147]Yamdagni; Kebarle *J. Am. Chem. Soc.* **1973,** *95*, 3504.

[148]For a review of the basicity and acidity of pyrroles, see Catalan; Abboud; Elguero *Adv. Heterocycl. Chem.* **1987,** *41*, 187-274.

show how careful one must be in attributing relative acidities or basicities to any particular effect.

For simple alcohols the order of gas-phase *acidity* is completely reversed from that in aqueous solution. In solution the acidity is in the order H_2O > $MeCH_2OH$ > Me_2CHOH > Me_3COH, but in the gas phase the order is precisely the opposite.[149] Once again solvation effects can be invoked to explain the differences. Comparing the two extremes, H_2O and Me_3COH, we see that the OH^- ion is very well solvated by water while the bulky Me_3CO^- is much more poorly solvated because the water molecules cannot get as close to the oxygen. Thus in solution H_2O gives up its proton more readily. When solvent effects are absent, however, the intrinsic acidity is revealed and Me_3COH is a stronger acid than H_2O. This result demonstrates that simple alkyl groups cannot be simply regarded as electron-donating. If methyl is an electron-donating group, then Me_3COH should be an intrinsically weaker acid than H_2O, yet it is stronger. A similar pattern is found with carboxylic acids, where simple aliphatic acids such as propanoic are stronger than acetic acid in the gas phase,[150] though weaker in aqueous solution (Table 8.4). The evidence in these and other cases[151] is that alkyl groups can be electron-donating when connected to unsaturated systems but in other systems may have either no effect or may actually be electron-withdrawing. The explanation given for the intrinsic gas-phase acidity order of alcohols as well as the basicity order of amines is that alkyl groups, because of their polarizability, can spread both positive and negative charges.[152] It has been calculated that even in the case of alcohols the field effects of the alkyl groups are still operating normally, but are swamped by the greater polarizability effects.[153] Polarizability effects on anionic centers are a major factor in gas-phase acid–base reactions.[154]

It has been shown (by running reactions on ions that are solvated in the gas phase) that solvation by even one molecule of solvent can substantially affect the order of basicities.[155]

An important aspect of solvent effects is the effect on the orientation of solvent molecules when an acid or base is converted to its conjugate. For example, consider an acid RCOOH converted to $RCOO^-$ in aqueous solution. The solvent molecules, by hydrogen bonding, arrange themselves around the COO^- group in a much more orderly fashion than they had been arranged around the COOH group (because they are more strongly attracted to the negative charge). This represents a considerable loss of freedom and a decrease in entropy. Thermodynamic measurements show that for simple aliphatic and halogenated aliphatic acids in aqueous solution at room temperature, the entropy ($T\Delta S$) usually contributes much more to the total free-energy change ΔG than does the enthalpy ΔH.[156] Two examples are shown in Table 8.6.[157] Resonance and field effects of functional groups therefore affect the acidity of RCOOH in two distinct ways. They affect the enthalpy (electron-withdrawing

[149] Baird *Can. J. Chem.* **1969,** *47,* 2306; Brauman; Blair, Ref. 70; Arnett; Small; McIver; Miller *J. Am. Chem. Soc.* **1974,** *96,* 5638; Blair; Isolani; Riveros *J. Am. Chem. Soc.* **1973,** *95,* 1057; McIver; Scott; Riveros *J. Am. Chem. Soc.* **1973,** *95,* 2706. The alkylthiols behave similarly; gas-phase acidity increases with increasing group size while solution (aqueous) acidity decreases: Bartmess; McIver *J. Am. Chem. Soc.* **1977,** *99,* 4163.

[150] For a table of gas-phase acidities of 47 simple carboxylic acids, see Caldwell; Renneboog; Kebarle *Can. J. Chem.* **1989,** *67,* 611.

[151] Brauman; Blair *J. Am. Chem. Soc.* **1971,** *93,* 4315; Kwart; Takeshita *J. Am. Chem. Soc.* **1964,** *86,* 1161; Fort; Schleyer *J. Am. Chem. Soc.* **1964,** *86,* 4194; Holtz; Stock *J. Am. Chem. Soc.* **1965,** *87,* 2404; Laurie; Muenter *J. Am. Chem. Soc.* **1966,** *88,* 2883.

[152] Brauman; Blair, Ref. 70; Munson, Ref. 144; Brauman; Riveros; Blair, Ref. 144; Huheey *J. Org. Chem.* **1971,** *36,* 204; Radom *Aust. J. Chem.* **1975,** *28,* 1; Aitken; Bahl; Bomben; Gimzewski; Nolan; Thomas *J. Am. Chem. Soc.* **1980,** *102,* 4873.

[153] Taft; Taagepera; Abboud; Wolf; DeFrees; Hehre; Bartmess; McIver *J. Am. Chem. Soc.* **1978,** *100,* 7765. For a scale of polarizability parameters, see Hehre; Pau; Headley; Taft; Topsom *J. Am. Chem. Soc.* **1986,** *108,* 1711.

[154] Bartmess; Scott; McIver *J. Am. Chem. Soc.* **1979,** *101,* 6056.

[155] Bohme; Rakshit; Mackay *J. Am. Chem. Soc.* **1982,** *104,* 1100.

[156] Bolton; Hepler, Ref. 115; Ref. 71. See also Wilson; Georgiadis; Bartmess *J. Am. Chem. Soc.* **1991,** *113,* 1762.

[157] Bolton; Hepler, Ref. 115, p. 529; Hambly, Ref. 71, p. 92.

TABLE 8.6 Thermodynamic values for the ionizations of acetic and chloroacetic acids in H_2O at 25°C[157]

		ΔG		ΔH		$T\Delta S$	
Acid	**pK_a**	**kcal/mol**	**kJ/mole**	**kcal/mole**	**kJ/mol**	**kcal/mol**	**kJ/mol**
CH_3COOH	4.76	+6.5	+27	−0.1	−0.4	−6.6	−28
$ClCH_2COOH$	2.86	+3.9	+16	−1.1	−4.6	−5.0	−21
Cl_3CCOOH	0.65	+0.9	+3.8	+1.5	+6.3	+0.6	+2.5

groups increase acidity by stabilizing $RCOO^-$ by charge dispersal), but they also affect the entropy (by lowering the charge on the COO^- group and by changing the electron-density distribution in the COOH group, electron-withdrawing groups alter the solvent orientation patterns around both the acid and the ion, and consequently change ΔS).

A change from a protic to an aprotic solvent can also affect the acidity or basicity, since there is a difference in solvation of anions by a protic solvent (which can form hydrogen bonds) and an aprotic one.[158] The effect can be extreme: in DMF, picric acid is stronger than HBr,[159] though in water HBr is far stronger. This particular result can be attributed to size. That is, the large ion $(O_2N)_3C_6H_2O^-$ is better solvated by DMF than the smaller ion Br^-.[160] The ionic strength of the solvent also influences acidity or basicity, since it has an influence on activity coefficients.

In summary, solvation can have powerful effects on acidity and basicity. In the gas phase the effects discussed in the previous section, especially resonance and field effects, operate unhindered by solvent molecules. As we have seen, electron-withdrawing groups generally increase acidity (and decrease basicity); electron-donating groups act in the opposite way. In solution, especially aqueous solution, these effects still largely persist (which is why pK values in Table 8.4 do largely correlate with resonance and field effects), but in general are much weakened, and occasionally reversed.[119]

[158]For a review, see Parker *Q. Rev., Chem. Soc.* **1962,** *16,* 163-187.
[159]Sears; Wolford; Dawson *J. Electrochem. Soc.* **1956,** *103,* 633.
[160]Miller; Parker *J. Am. Chem. Soc.* **1961,** *83,* 117.