CHAPTER 7

Irradiation Processes in Organic Chemistry

Most reactions carried out in organic chemistry laboratories take place between molecules all of which are in their ground electronic states. In a *photochemical reaction*,[1] however, a reacting molecule has been previously promoted by absorption of light to an electronically excited state. A molecule in an excited state must lose its extra energy in some manner; it cannot remain in the excited condition for long. The subject of electronic spectra is closely related to photochemistry. A chemical reaction is not the only possible means of relinquishing the extra energy in a photochemical process. In this chapter, first we discuss electronically excited states and the processes of promotion to these states. Two other methods are available to facilitate chemical reactions: sonochemistry and microwave chemistry. Although the physical processes involved are not necessarily the same excitation processes observed in photochemistry, irradiation with ultrasound or with microwaves have a significant influence on chemical reactivity. For that reason, they are included in this chapter.

[1] There are many books on photochemistry. Some recent ones are Michl, J.; Bonačić-Koutecký, V. *Electronic Aspects of Organic Photochemistry*, Wiley, NY, ***1990***; Scaiano, J.C. *Handbook of Organic Photochemistry*, 2 vols., CRC Press, Boca Raton, FL, ***1989***; Coxon, J.M.; Halton, B. *Organic Photochemistry*, 2nd ed.; Cambridge University Press: Cambridge, ***1987***; Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, *Introduction to Organic Photochemistry*, Wiley, NY, ***1986***; Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***; Margaretha, P. *Preparative Organic Photochemistry*, *Top. Curr. Chem.* ***1982***, *103*; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, ***1978***; Rohatgi-Mukherjee. K.K. *Fundamentals of Photochemistry*, Wiley, NY, ***1978***; Barltrop, J.A.; Coyle, J.D. *Principles of Photochemistry*, Wiley, NY, ***1978***. For a comprehensive older treatise, see Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***. For a review of the photochemistry of radicals and carbenes, see Scaiano, J.; Johnston, L.J. *Org. Photochem.* ***1989***, *10*, 309. For a history of photochemistry, see Roth, H.D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1193. For a glossary of terms used in photochemistry, see Braslavsky, S.E.; Houk, K.N. *Pure Appl. Chem.* ***1988***, *60*, 1055. See also, the series, *Advances in Photochemistry*, *Organic Photochemistry*, and *Excited States*.

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PHOTOCHEMISTRY

Excited States and the Ground State

Electrons can move from the ground-state energy level of a molecule to a higher level (i.e., an unoccupied orbital of higher energy) if outside energy is supplied. In a photochemical process, this energy is in the form of light. Light of any wavelength has associated with it an energy value given by $E = h\nu$, where n is the frequency of the light ($n =$ velocity of light c divided by the wavelength λ) and h is Planck's constant. Since the energy levels of a molecule are quantized, the amount of energy required to raise an electron in a given molecule from one level to a higher one is a fixed quantity. Only light with exactly the frequency corresponding to this amount of energy will cause the electron to move to the higher level. If light of another frequency (too high or too low) is sent through a sample, it will pass out without a loss in intensity, since the molecules will not absorb it. However, if light of the correct frequency is passed in, the energy will be used by the molecules for electron promotion, and hence the light that leaves the sample will be diminished in intensity or altogether gone. A *spectrophotometer* is an instrument that allows light of a given frequency to pass through a sample and that detects (by means of a phototube) the amount of light that has been transmitted, that is, not absorbed. A spectrophotometer compares the intensity of the transmitted light with that of the incident light. Automatic instruments gradually and continuously change the frequency, and an automatic recorder plots a graph of absorption versus frequency or wavelength.

The energy of electronic transitions corresponds to light in the visible, UV, and far-UV regions of the spectrum (Fig. 7.1). Absorption positions are normally expressed in wavelength units, usually nanometers (nm).[2] If a compound absorbs in the visible, it is colored, possessing a color complementary to that which is absorbed.[3] Thus a compound absorbing in the violet is yellow. The far-uv region is studied by organic chemists less often than the visible or ordinary uv regions because special vacuum instruments are required owing to the fact that oxygen and nitrogen absorb in these regions.

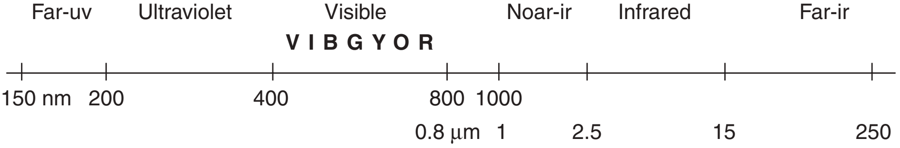

Fig. 7.1. The uv, visible, and ir portions of the electromagnetic spectrum.

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[2] Formerly, millimicrons (mμ) were frequently used; numerically they are the same as nanometers.

[3] For monographs, see Zollinger, H. *Color Chemistry*, VCH, NY, ***1987***; Gordon, P.F.; Gregory, P. *Organic Chemistry in Colour*, Springer, NY, ***1983***; Griffiths, J. *Colour and Constitution of Organic Molecules*, Academic Press, NY, ***1976***. See also, Fabian, J.; Zahradník, R. *Angew. Chem. Int. Ed.* ***1989***, *28*, 677.

From these considerations it would seem that an electronic spectrum should consist of one or more sharp peaks, each corresponding to the transfer of an electron from one electronic level to another. Under ordinary conditions the peaks are seldom sharp. In order to understand why, it is necessary to realize that molecules are constantly vibrating and rotating and that these motions are also quantized. A molecule at any time is not only in a given electronic state but also in a given vibrational and rotational state. The difference between two adjacent vibrational levels is much smaller than the difference between adjacent electronic levels, and the difference between adjacent rotational levels is smaller still. A typical situation is shown in Fig. 7.2. When an electron moves from one electronic level to another, it moves from a given vibrational and rotational level within that electronic level to some vibrational and rotational level at the next electronic level. A given sample contains a large number of molecules, and even if all of them are in the ground electronic state, they are still distributed among the vibrational and rotational states (though the ground vibrational state V_0 is most heavily populated). This means that not just one wavelength of light will be absorbed, but a number of them close together, with the most probable transition causing the most intense peak. But in molecules containing more than a few atoms there are so many possible transitions and these are so close together that what is observed is a relatively broad band. The height of the peak depends on the number of molecules making the transition and is proportional to log ε, where ε is the *extinction coefficient*. The extinction coefficient can be expressed by $\varepsilon = E/cl$, where c is the concentration in moles per liter, l is the

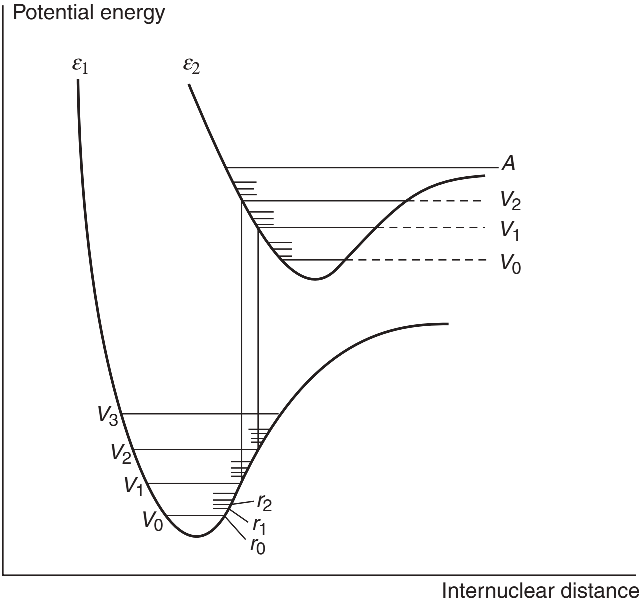

Fig. 7.2. Energy curves for a diatomic molecule. Two possible transitions are shown. When an electron has been excited to the point marked A, the molecule may cleave (p. 335).

cell length in centimeters, and $E = \log I_0/I$, where I_0 is the intensity of the incident light and I of the transmitted light. The wavelength is usually reported as λ_{max}, meaning that this is the top of the peak. Purely vibrational transitions, such as between V_0 and V_1 of E_1, which require much less energy, are found in the ir region and are the basis of ir spectra. Purely rotational transitions are found in the far-ir and microwave (beyond the far-ir) regions.

A UV or visible absorption peak is caused by the promotion of an electron in one orbital (usually a ground-state orbital) to a higher orbital. Normally, the amount of energy necessary to make this transition depends mostly on the nature of the two orbitals involved and much less on the rest of the molecule. Therefore, a simple functional group such as the C=C double bond always causes absorption in the same general area. A group that causes absorption is called a *chromophore*.

Singlet and Triplet States: "Forbidden" Transitions

In most organic molecules, all electrons in the ground state are paired, with each member of a pair possessing opposite spin as demanded by the Pauli principle. When one of a pair of electrons is promoted to an orbital of higher energy, the two electrons no longer share an orbital, and the promoted electron may, in principle, have the same spin as its former partner or the opposite spin. As we saw in Chapter 5, a molecule in which two unpaired electrons have the same spin is called a *triplet*,[4] while one in which all spins are paired is a *singlet*. Thus, at least in principle, for every excited singlet state there is a corresponding triplet state. In most cases, the triplet state has a lower energy than the corresponding singlet, which is in accord with Hund's rule. Therefore, a different amount of energy, and hence a different wavelength is required to promote an electron from the ground state (which is almost always a singlet) to an excited singlet than to the corresponding triplet state.

It would thus seem that promotion of a given electron in a molecule could result either in a singlet or a triplet excited state depending on the amount of energy added. However, this is often not the case because transitions between energy levels are governed by selection rules, which state that certain transitions are "forbidden." There are several types of "forbidden" transitions, two of which are more important than the others.

1. *Spin-Forbidden Transitions*. Transitions in which the spin of an electron changes are not allowed, because a change from one spin to the opposite involves a change in angular momentum and such a change would violate the law of conservation of angular momentum. Therefore, singlet–triplet and triplet–singlet transitions are forbidden, whereas singlet–singlet and triplet–triplet transitions are allowed.
2. *Symmetry-Forbidden Transitions*. Among the transitions in this class are those in which a molecule has a center of symmetry. In such cases, a $g \rightarrow g$ or

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[4] See Kurreck, H. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1409 for a brief discussion of the triplet state in organic chemistry.

$u \rightarrow u$ transition (see p. 5) is "forbidden," while a $g \rightarrow u$ or $u \rightarrow g$ transition is allowed.

We have put the word "forbidden" into quotation marks because these transitions are not actually forbidden but only highly improbable. In most cases, promotions from a singlet ground state to a triplet excited state are so improbable that they cannot be observed, and it is safe to state that in most molecules only singlet–singlet promotions take place. However, this rule does break down in certain cases, most often when a heavy atom (e.g., iodine) is present in the molecule, in which cases it can be shown from spectra that singlet–triplet promotions are occurring.[5] Symmetry-forbidden transitions can frequently be observed, though usually with low intensity.

Types of Excitation

When an electron in a molecule is promoted (normally only one electron in any molecule), it usually goes into the lowest available vacant orbital, though promotion to higher orbitals is also possible. For most organic molecules, there are consequently four types of electronic excitation:

1. $\sigma \rightarrow \sigma^*$. Alkanes, which have no n or π electrons, can be excited only in this way.[6]
2. $n \rightarrow \sigma^*$. Alcohols, amines,[7] ethers, and so on, can also be excited in this manner.
3. $\pi \rightarrow \pi^*$. This pathway is open to alkenes as well as to aldehydes, carboxylic esters, and so on.
4. $n \rightarrow \pi^*$. Aldehydes, ketones, carboxylic esters, and so on, can undergo this promotion as well as the other three.

The four excitation types above are listed in what is normally the order of decreasing energy. Thus light of the highest energy (in the far uv) is necessary for $\sigma \rightarrow \sigma^*$ excitation, while $n \rightarrow \pi^*$ promotions are caused by ordinary uv light. However, the order may sometimes be altered in some solvents.

In 1,3-butadiene (and other compounds with two conjugated double bonds) there are two π and two π^* orbitals (p. 39). The energy difference between the higher $\pi(\chi_2)$ and the lower $\pi^*(\chi_3)$ orbital is less than the difference between the π and π^* orbitals of ethylene. Therefore 1,3-butadiene requires less energy than ethylene, and thus light of a higher wavelength, to promote an electron. This is a general phenomenon, and it may be stated that, in general, *the more conjugation in a molecule, the more the absorption is displaced toward higher wavelengths* (see Table 7.1).[8]

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[5] For a review of photochemical heavy-atom effects, see Koziar, J.C.; Cowan, D.O. *Acc. Chem. Res.* ***1978***, *11*, 334.

[6] An n electron is one in an unshared pair.

[7] For a review of the photochemistry of amines, see Malkin, Yu.N.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1985***, *54*, 1041.

[8] Bohlmann, F.; Mannhardt, H. *Chem. Ber.* ***1956***, *89*, 1307.

TABLE 7.1. Ultraviolet Absorption[8] of CH_3–$(CH{=}CH)_n$–CH_3 for Some Values of n

n	nm
2	227
3	263
6	352
9	413

When a chromophore absorbs at a certain wavelength and the substitution of one group for another causes absorption at a longer wavelength, a *bathochromic shift* is said to have occurred. The opposite kind of shift is called *hypsochromic*.

Of the four excitation types listed above, the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ are far more important in organic photochemistry than the other two. Compounds containing C=O groups can be excited in both ways, giving rise to at least two peaks in the UV.

As we have seen, a chromophore is a group that causes a molecule to absorb light. Examples of chromophores in the visible or UV are C=O, N=N,[9] Ph, and NO_2. Some chromophores in the far UV (beyond 200 nm) are C=C, C≡C, Cl, and OH. An *auxochrome* is a group that displaces (through resonance) and usually intensifies the absorption of a chromophore present in the same molecule. Groups, such as Cl, OH, and NH_2, are generally regarded as auxochromes since they shift (usually bathochromically) the uv and visible bands of chromophores, such as Ph or C=O (see Table 7.2).[10] Since auxochromes are themselves chromophores

TABLE 7.2. Some UV Peaks of Substituted Benzenes in Water, or Water With a Trace of Methanol (for Solubility)[a]

	Primary Band		Secondary Band	
	λ_{max}, nm	ε_{max}	λ_{max}, nm	ε_{max}
PhH	203.5	7,400	254	204
PhCl	209.5	7,400	263.5	190
PhOH	210.5	6,200	270	1,450
PhOMe	217	6,400	269	1,480
PhCN	224	13,000	271	1,000
PhCOOH	230	11,600	273	970
$PhNH_2$	230	8,600	280	1,430
PhO^-	235	9,400	287	2,600
PhAc	245.5	9,800		
PhCHO	249.5	11,400		
$PhNO_2$	268.5	7,800		

[a] Note how auxochromes shift and usually intensify the peaks.

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[9] For a review of the azo group as a chromophore, see Rau, H. *Angew. Chem. Int. Ed.* 1973, *12*, 224.

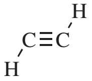
[10] These values are from Jaffé, H.H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*, Wiley, NY, ***1962***, p. 257.

(to be sure, generally in the far-UV), it is sometimes difficult to decide which group in a molecule is an auxochrome and which a chromophore. For example, in acetophenone (PhCOMe) is the chromophore Ph or C=O? In such cases, the distinction becomes practically meaningless.

Nomenclature and Properties of Excited States

An excited state of a molecule can be regarded as a distinct chemical species, different from the ground state of the same molecule and from other excited states. It is obvious that we need some method of naming excited states. Unfortunately, there are several methods in use, depending on whether one is primarily interested in photochemistry, spectroscopy, or molecular-orbital theory.[11] One of the most common methods simply designates the original and newly occupied orbitals, with or without a superscript to indicate singlet or triplet. Thus the singlet state arising from promotion of a π to a π^* orbital in ethylene would be the $^1(\pi,\pi^*)$ state or the π,π^* singlet state. Another very common method can be used even in cases where one is not certain which orbitals are involved. The lowest energy excited state is called S_1, the next S_2, and so on, and triplet states are similarly labeled T_1, T_2, T_3, and so on. In this notation, the ground state is S_o. Other notational systems exist, but in this book we will confine ourselves to the two types just mentioned.

The properties of excited states are not easy to measure because of their generally short lifetimes and low concentrations, but enough work has been done for us to know that they often differ from the ground state in geometry, dipole moment and acid or base strength.[12] For example, acetylene, which is linear in the ground state, has a trans geometry in the excited state



with $\sim sp^2$ carbons in the $^1(\pi,\pi^*)$ state.[13] Similarly, the $^1(\pi,\pi^*)$ and the $^3(\pi,\pi^*)$ states of ethylene have a perpendicular and not a planar geometry,[14] and the $^1(n,\pi^*)$ and $^3(n,\pi^*)$ states of formaldehyde are both pyramidal.[15] Triplet species tend to stabilize themselves by distortion, which relieves interaction between the

[11] For discussions of excited-state notation and other terms in photochemistry, see Pitts, Jr., J.N.; Wilkinson, F.; Hammond, G.S. *Adv. Photochem.* ***1963***, *1*, 1; Porter, G.B.; Balzani, V.; Moggi, L. *Adv. Photochem.* ***1974***, *9*, 147. See also, Braslavsky, S.E.; Houk, K.N. *Pure Appl. Chem.* ***1988***, *60*, 1055.

[12] For reviews of the structures of excited states, see Zink, J.I.; Shin, K.K. *Adv. Photochem.* ***1991***, *16*, 119; Innes, K.K. *Excited States* ***1975***, *2*, 1; Hirakawa, A.Y.; Masamichi, T. *Vib. Spectra Struct.* ***1983***, *12*, 145.

[13] Ingold, C.K.; King, G.W. *J. Chem. Soc.* ***1953***, 2702, 2704, 2708, 2725, 2745. For a review of acetylene photochemistry, see Coyle, J.D. *Org. Photochem.* ***1985***, *7*, 1.

[14] Merer, A.J.; Mulliken, R.S. *Chem. Rev.* ***1969***, *69*, 639.

[15] Robinson, G.W.; Di Giorgio, V.E. *Can. J. Chem.* ***1958***, *36*, 31; Buenker, R.J.; Peyerimhoff, S.D. *J. Chem. Phys.* ***1970***, *53*, 1368; Garrison, B.J.; Schaefer III, H.F.; Lester, Jr., W.A. *J. Chem. Phys.* ***1974***, *61*, 3039; Streitwieser, Jr., A.; Kohler, B. *J. Am. Chem. Soc.* ***1988***, *110*, 3769. For reviews of excited states of formaldehyde, see Buck, H.M. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 193, 225; Moule, D.C.; Walsh, A.D. *Chem. Rev.* ***1975***, *75*, 67.

TABLE 7.3. Typical Energies for Some Covalent Single Bonds (see Table 1.7) and the Corresponding Approximate Wavelengths

	E		
Bond	kcal mol^{-1}	kJ mol^{-1}	nm
C—H	95	397	300
C—O	88	368	325
C—C	83	347	345
Cl—Cl	58	243	495
C—O	35	146	820

unpaired electrons. Obviously, if the geometry is different, the dipole moment will probably differ also and the change in geometry and electron distribution often results in a change in acid or base strength.[16] For example, the S_1 state of 2-naphthol is a much stronger acid (p*K* 3.1) than the ground state (S_0) of the same molecule (p*K* 9.5).[17]

Photolytic Cleavage

We have said that when a molecule absorbs a quantum of light, it is promoted to an excited state. Actually, that is not the only possible outcome. Because the energy of visible and UV light is of the same order of magnitude as that of covalent bonds (Table 7.3), another possibility is that the molecule may cleave into two parts, a process known as *photolysis*. There are three situations that can lead to cleavage:

1. The promotion may bring the molecule to a vibrational level so high that it lies above the right-hand portion of the E_2 curve (line *A* in Fig. 7.2). In such a case, the excited molecule cleaves at its first vibration.
2. Even where the promotion is to a lower vibrational level, one which lies wholly within the E_2 curve (e.g., V_1 or V_2), the molecule may still cleave. As Fig. 7.2 shows, equilibrium distances are greater in excited states than in the ground state. The *Franck–Condon principle* states that promotion of an electron takes place much faster than a single vibration (the promotion takes $\sim 10^{-15}$ s; a vibration $\sim 10^{-12}$ s). Therefore, when an electron is suddenly promoted, even to a low vibrational level, the distance between the atoms is essentially unchanged and the bond finds itself in a compressed condition like a pressed-in spring; this condition may be relieved by an outward surge that is sufficient to break the bond.

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[16] For a review of acid–base properties of excited states, see Ireland, J.F.; Wyatt, P.A.H. *Adv. Phys. Org. Chem.* ***1976***, *12*, 131.

[17] Weller, A. *Z. Phys. Chem. (Frankfurt am Main)* ***1955***, *3*, 238, *Discuss. Faraday Soc.* ***1959***, *27*, 28.

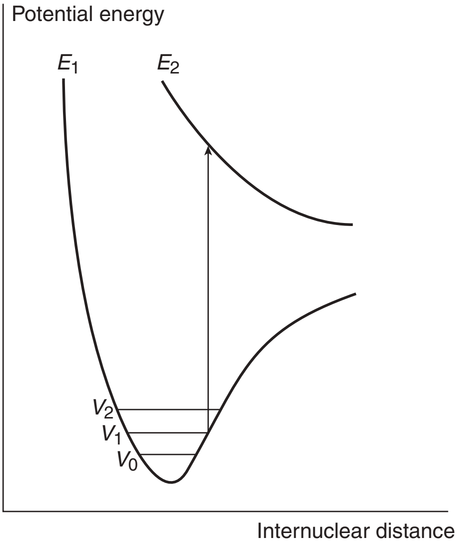

Fig. 7.3. Promotion to a dissociative state results in bond cleavage.

3. In some cases, the excited state is entirely dissociative (Fig. 7.3), that is, there is no distance where attraction outweighs repulsion, and the bond must cleave. An example is the hydrogen molecule, where a $\sigma \rightarrow \sigma*$ promotion always results in cleavage.

A photolytic cleavage can break the molecule into two smaller molecules or into two free radicals (see p. 343). Cleavage into two ions, though known, is much rarer. Once free radicals are produced by a photolysis, they behave like free radicals produced in any other way (Chapter 5) except that they may be in excited states, and this can cause differences in behavior.[18]

The Fate of the Excited Molecule: Physical Processes

When a molecule has been photochemically promoted to an excited state, it does not remain there for long. Most promotions are from the S_o to the S_1 state. As we have seen, promotions from S_o to triplet states are "forbidden." Promotions to S_2 and higher singlet states take place, but in liquids and solids these higher states usually drop very rapidly to the S_1 state ($\sim 10^{-13}$–10^{-11} s). The energy lost when an S_2 or S_3 molecule drops to S_1 is given up in small increments to the environment by collisions with neighboring molecules. Such a process is called an *energy cascade*. In a similar manner, the initial excitation and the decay from higher singlet states initially populate many of the vibrational levels of S_1, but these also cascade, down to the lowest vibrational level of S_1. Therefore, in most cases, the lowest

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[18] Lubitz, W.; Lendzian, F.; Bittl, R. *Acc. Chem. Res.* ***2002***, *35*, 313.

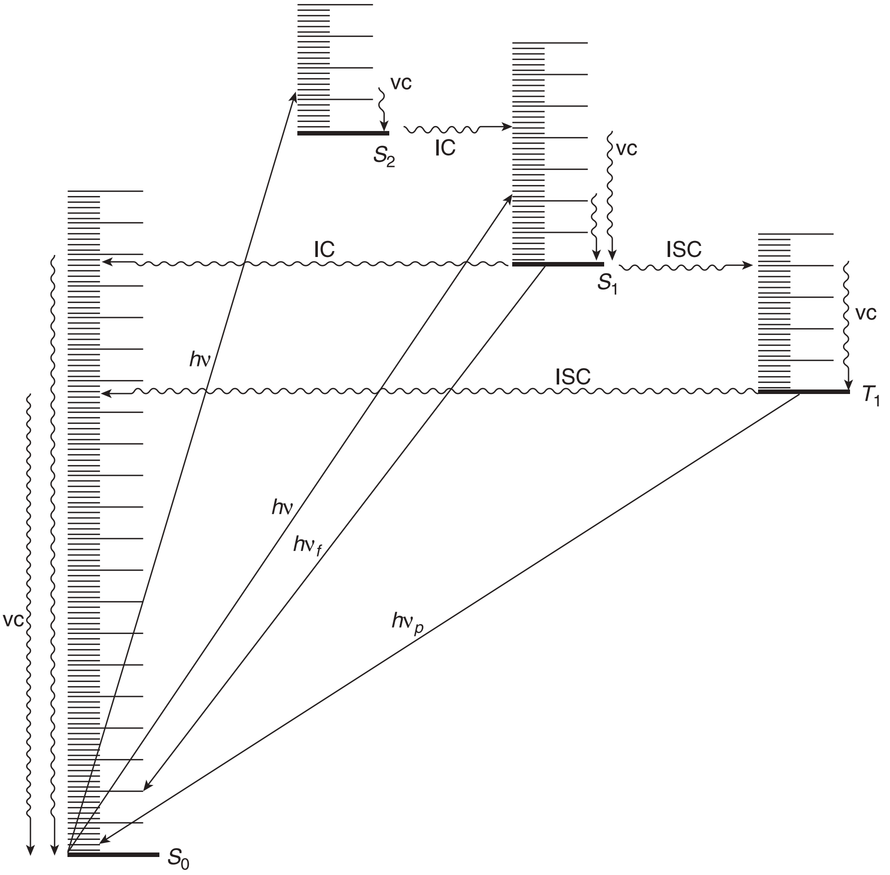

Fig. 7.4. Modified Jablonski diagram showing transitions between excited states and the ground state. Radiative processes are shown by straight lines, radiationless processes by wavy lines. vc = vibrational cascade; $h\nu_f$ = fluorescence; $h\nu_p$ = phosphorescence.

vibrational level of the S_1 state is the only important excited singlet state.[19] This state can undergo various physical and chemical processes. In the following list, we describe the physical pathways open to molecules in the S_1 and excited triplet states. These pathways are also shown in a modified Jablonski diagram (Fig. 7.4) and in Table 7.4.

1. A molecule in the S_1 state can cascade down through the vibrational levels of the S_0 state and thus return to the ground state by giving up its energy in small increments to the environment, but this is generally quite slow because the

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[19] For a review of physical and chemical processes undergone by higher states, see Turro, N.J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* ***1978***, *78*, 125.

TABLE 7.4. Physical Processes Undergone by Excited Molecules[a]

$S_0 + h\nu \rightarrow S_1^{\mathrm{v}}$	Excitation
S_1^{v}	$\rightsquigarrow \rightarrow S_1 + \Delta$ Vibrational relaxation
$S_1 \rightarrow S_1 + h\nu$	Fluorescence
S_1	$\rightsquigarrow \rightarrow S_0 + \Delta$ Internal conversion
$S_1 \rightsquigarrow T_1^{\mathrm{v}}$	Intersystem crossing
$T_1^{\mathrm{v}} \rightsquigarrow T_1 + \Delta$	Vibrational relaxation
$T_1 \rightarrow S_0 + h\nu$	Phosphorescence
$T_1 \rightsquigarrow S_0 + \Delta$	Intersystem crossing
$S_1 + A_{(S_0)} \rightarrow S_0 + A_{(S_1)}$	Singlet–singlet transfer (photosensitization)
$T_1 + A_{(S_0)} \rightarrow S_0 + A_{(T_1)}$	Triplet–triplet transfer (photosensitization)

[a] The superscript v indicates vibrationally excited state: excited states higher than S_1 or T_1 are omitted.

amount of energy is large. The process is called *internal conversion* (IC, see Fig. 7.4). Because it is slow, most molecules in the S_1 state adopt other pathways.[20]

2. A molecule in the S_1 state can drop to some low vibrational level of the S_o state all at once by giving off the energy in the form of light. This process, which generally happens within 10^{-9} s, is called *fluorescence*. This pathway is not very common either (because it is relatively slow), except for small molecules, for example, diatomic, and rigid molecules, for example, aromatic. For most other compounds, fluorescence is very weak or undetectable. For compounds that do fluoresce, the fluorescence emission spectra are usually the approximate mirror images of the absorption spectra. This comes about because the fluorescing molecules all drop from the lowest vibrational level of the S_1 state to various vibrational levels of S_o, while excitation is from the lowest vibrational level of S_o to various levels of S_1 (Fig. 7.5). The only peak in common is the one (called the 0–0 peak) that results from transitions between the lowest vibrational levels of the two states. In solution, even the 0–0 peak may be noncoincidental because the two states are solvated differently. Fluorescence nearly always arises from a $S_1 \rightarrow S_0$ transition, though azulene (p. $$$) and its simple derivatives are exceptions,[21] emitting fluorescence from $S_2 \rightarrow S_0$ transitions.

Because of the possibility of fluorescence, any chemical reactions of the S_1 state must take place very fast, or fluorescence will occur before they can happen.

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[20] For a monograph on radiationless transitions, see Lin, S.H. *Radiationless Transitions*; Academic Press, NY, ***1980***. For reviews, see Kommandeur, J. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 421; Freed, K.F. *Acc. Chem. Res.* ***1978***, *11*, 74.

[21] For other exceptions, see Gregory, T.A.; Hirayama, F.; Lipsky, S. *J. Chem. Phys.* ***1973***, *58*, 4697; Sugihara, Y.; Wakabayashi, S.; Murata, I.; Jinguji, M.; Nakazawa, T.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* ***1985***, *107*, 5894, and references cited therein. See also Turro, N.J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* ***1978***, *78*, 125, see pp. 126–129.

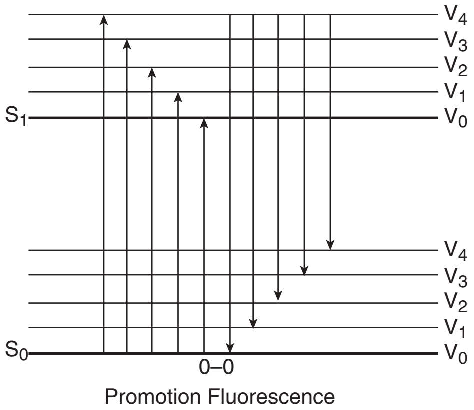

Fig. 7.5. Promotion and fluorescence between S_1 and S_0 states.

3. Most molecules (though by no means all) in the S_1 state can undergo an intersystem crossing (ISC, see Fig. 7.4) to the lowest triplet state T_1.[22] An important example is benzophenone, of which ~100% of the molecules that are excited to the S_1 state cross over to the T_1.[23] Intersystem crossing from singlet to triplet is of course a "forbidden" pathway, since the angular-momentum problem (p. 331) must be taken care of, but this often takes place by compensations elsewhere in the system. Intersystem crossings take place without loss of energy. Since a singlet state usually has a higher energy than the corresponding triplet, this means that energy must be given up. One way for this to happen is for the S_1 molecule to cross to a T_1 state at a high vibrational level and then for the T_1 to cascade down to its lowest vibrational level (see Fig. 7.4). This cascade is very rapid (10^{-12} s). When T_2 or higher states are populated, they too rapidly cascade to the lowest vibrational level of the T_1 state.
4. A molecule in the T_1 state may return to the S_o state by giving up heat (intersystem crossing) or light (this is called *phosphorescence*).[24] Of course, the angular-momentum difficulty exists here, so that both intersystem crossing and phosphorescence are very slow (~10^{-3}–10^{1} s). This means that T_1 states generally have much longer lifetimes than S_1 states. When they occur in the same molecule, phosphorescence is found at lower frequencies than fluorescence

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[22] Intersystem crossing from S_1 to T_2 and higher triplet states has also been reported in some aromatic molecules: Li, R.; Lim, E.C. *Chem. Phys.* ***1972***, *57*, 605; Sharf, B.; Silbey, R. *Chem. Phys. Lett.* ***1970***, *5*, 314. See also, Schlag, E.W.; Schneider, S.; Fischer, S.F. *Annu. Rev. Phys. Chem.* ***1971***, *22*, 465, pp. 490. There is evidence that ISC can also occur from the S_2 state of some molecules: Samanta, A. *J. Am. Chem. Soc.* ***1991***, *113*, 7427. Also see, Tanaka, R.; Kuriyama, Y.; Itoh, H.; Sakuragi, H.; Tokumaru, K. *Chem. Lett.* ***1993***, 1447; Ohsaku, M.; Koga, N.; Morokuma, K. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 71.

[23] Moore, W.M.; Hammond, G.S.; Foss, R.P. *J. Am. Chem. Soc.* ***1961***, *83*, 2789.

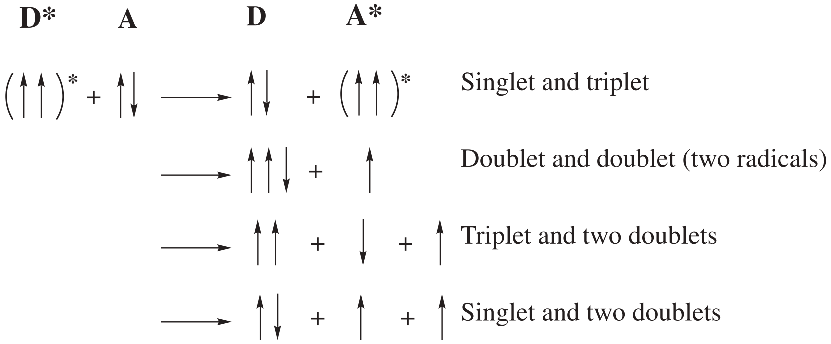
[24] For a review of physical processes of triplet states, see Lower, S.K.; El-Sayed, M.A. *Chem. Rev.* ***1966***, *66*, 199. For a review of physical and chemical processes of triplet states see Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21.

(because of the higher difference in energy between S_1 and S_0 than between T_1 and S_0) and is longer-lived (because of the longer lifetime of the T_1 state).

5. If nothing else happens to it first, a molecule in an excited state (S_1 or T_1) may transfer its excess energy all at once to another molecule in the environment, in a process called *photosensitization*.[25] The excited molecule (which we will call D for donor) thus drops to S_0 while the other molecule (A for acceptor) becomes excited:

$$D^* + A \longrightarrow A^* + D$$

Thus there are *two* ways for a molecule to reach an excited state: by absorption of a quantum of light or by transfer from a previously excited molecule.[26] The donor D is also called a *photosensitizer*. This energy transfer is subject to the *Wigner spin-conservation rule*, which is actually a special case of the law of conservation of momentum we encountered previously. According to the Wigner rule, the total electron spin does not change after the energy transfer. For example, when a triplet species interacts with a singlet these are some allowed possibilities:[27]



In all these cases, the products have three electrons spinning "up" and the fourth "down" (as do the starting molecules). However, formation of, say, two triplets (↑↓ + ↓↓) or two singlets (↑↓ + ↑↓), whether ground states or excited, would violate the rule.

In the two most important types of photosensitization, both of which are in accord with the Wigner rule, a triplet excited state generates another triplet and a singlet generates a singlet:

$$D_{T_1} + A_{S_0} \longrightarrow A_{T_1} + D_{S_0} \qquad \text{triplet–triplet transfer}$$

$$D_{S_1} + A_{S_0} \longrightarrow A_{S_1} + D_{S_0} \qquad \text{singlet–triplet transfer}$$

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[25] For reviews, see Albini, A. *Synthesis*, ***1981***, 249; Turro, N.J.; Dalton, J.C.; Weiss, D.S. *Org. Photochem.* ***1969***, *2*, 1.

[26] There is also a third way: in certain cases excited states can be produced directly in ordinary reactions. For a review, see White, E.H.; Miano, J.D.; Watkins, C.J.; Breaux, E.J. *Angew. Chem. Int. Ed.* ***1974***, *13*, 229.

[27] For another table of this kind, see Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, p. 89.

Singlet–singlet transfer can take place over relatively long distances (e.g., 40 Å), but triplet transfer normally requires a collision between the molecules.[28] Both types of photosensitization can be useful for creating excited states when they are difficult to achieve by direct irradiation. Photosensitization is therefore an important method for carrying out photochemical reactions when a molecule cannot be brought to the desired excited state by direct absorption of light. Triplet–triplet transfer is especially important because triplet states are usually much more difficult to prepare by direct irradiation than singlet states (often impossible) and because triplet states, having longer lifetimes, are much more likely than singlets to transfer energy by photosensitization. Photosensitization can also be accomplished by electron transfer.[29]

In choosing a photosensitizer, one should avoid a compound that absorbs in the same region as the acceptor because the latter will then compete for the light.[30] For examples of the use of photosensitization to accomplish reactions, see **15-62** and **15-63**.

6. An excited species can be quenched. Qunching is the deactivation of an excited molecular entity intermolecularly by an external environmental influence (e.g., a quencher) or intramolecularly by a substituent through a nonradiative process.[31] When the external environmental influence (quencher) interferes with the behavior of the excited state after its formation, the process is referred to as dynamic quenching. Common mechanisms include energy transfer, charge transfer, and so on. When the environmental influence inhibits the excited state formation the process is referred to as static quenching. A quencher is defined as a molecular entity that deactivates (quenches) an excited state of another molecular entity, either by energy tranfer, electron transfer, or by a chemical mechanism.[31]

An example is the rapid triplet quenching of aromatic ketone triplets by amines, which is well known.[32] Alkyl and aryl thiols and thioethers also serve as quenchers in this system[33] In this latter case, the mechanism involves electron

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[28] Long-range triplet-triplet transfer has been observed in a few cases: Bennett, R.G.; Schwenker, R.P.; Kellogg, R.E. *J. Chem. Phys.* ***1964***, *41*, 3040; Ermolaev, V.L.; Sveshnikova, E.B. *Izv. Akad. Nauk SSSR, Ser. Fiz.* ***1962***, *26*, 29 [*C. A.* ***1962***, *57*, 1688], *Opt. Spectrosc. (USSR)* ***1964***, *16*, 320.

[29] For a review, see Kavarno, G.J.; Turro, N.J. *Chem. Rev.* ***1986***, *86*, 401. See also, Mariano, P.S. *Org. Photochem.* ***1987***, *9*, 1.

[30] For a review of other complications that can take place in photosensitized reactions, see Engel, P.S.; Monroe, B.M. *Adv. Photochem.* ***1971***, *8*, 245.

[31] Verhoeven, J.W. *Pure Appl. Chem.* ***1996***, *68*, 2223 (see p 2268).

[32] See Aspari, P.; Ghoneim, N.; Haselbach, E.; von Raumer, M.; Suppan, P.; Vauthey, E. *J. Chem. Soc., Faraday Trans.* ***1996***, *92*, 1689; Cohen, S.G.; Parola, A.; Parsons, Jr., G.H. *Chem. Rev.* ***1973***, *73*, 141; Inbar, S.; Linschitz, H.; Cohen, S.G. *J. Am. Chem. Soc.* ***1981***, *103*, 1048; Peters, K.S.; Lee, J. *J. Phys. Chem.* ***1993***, *97*, 3761; von Raumer, M.; Suppan, P.; Haselbach, E. *Helv. Chim. Acta* ***1997***, *80*, 719.

[33] Guttenplan, J.B.; Cohen, S.G. *J. Org. Chem.* ***1973***, *38*, 2001; Inbar, S.; Linschitz, H.; Cohen, S.G. *J. Am. Chem. Soc.* ***1982***, *104*, 1679; Bobrowski, K.; Marciniak, B.; Hug, G.L. *J. Photochem. Photobiol. A: Chem.* ***1994***, *81*, 159; Wakasa, M.; Hayashi, H. *J. Phys. Chem.* ***1996***, *100*, 15640.

transfer from the sulfur atom to the triplet ketone, and this is supported by theoretical calculations.[34] Aromatic ketone triplets are quenched by phenols and the photochemical reaction between aromatic ketones and phenols is efficient only in the presence of an acid catalyst.[35] Indirect evidence has been provided for involvement of the hydrogen-bonded triplet exciplex and for the role of electron transfer in this reaction.[36]

The Fate of the Excited Molecule: Chemical Processes

Although both excited singlet and triplet species can undergo chemical reactions, they are much more common for triplets, simply because these generally have much longer lifetimes. Excited singlet species, in most cases, have a lifetime of $<10^{-10}$ s and undergo one of the physical processes already discussed before they have a chance to react chemically. Therefore, photochemistry is largely the chemistry of triplet states.[37] Table 7.5[38] lists many of the possible chemical pathways that can be taken by an excited molecule.[39] The first four of these are unimolecular reactions; the others are bimolecular. In the case of bimolecular reactions, it is rare for two excited molecules to react with each other (because the concentration of excited molecules at any one time is generally low); reactions are between an excited molecule and an unexcited molecule of either the same or another species. The reactions listed in Table 7.5 are primary processes. Secondary reactions often follow, since the primary products are frequently radicals or carbenes; even if they are ordinary molecules, they are often in upper vibrational levels and so have excess energy. In almost all cases, the primary products of photochemical reactions are in their ground states, though exceptions are known.[40] Of the reactions listed in Table 7.5, the most common are cleavage into radicals (1), decomposition into molecules (2), and (in the presence of a suitable acceptor molecule) photosensitization (7), which we have already discussed. The following are some specific examples of reaction categories (1)–(6). Other examples are discussed in Part 2 of this book.[41]

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[34] Marciniak, B.; Bobrowski, K.; Hug, G.L. *J. Phys. Chem.* ***1993***, *97*, 11937.

[35] Becker, H.-D. *J. Org. Chem.* ***1967***, *32*, 2115; J. *Org. Chem.* ***1967***, *32*, 2124; *J. Org. Chem.* ***1967***, *32*, 2140.

[36] Lathioor, E.C.; Leigh, W.J.; St. Pierre, M.J. *J. Am. Chem. Soc.* ***1999***, *121*, 11984.

[37] For a review of the chemical reactions of triplet states, see Wagner, P.J.; Hammond, G.S. Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21. For other reviews of triplet states, see *Top. Curr. Chem.* ***1975***, Vols. 54 and 55.

[38] Adapted from Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, p. 367.

[39] For a different kind of classification of photochemical reactions, see Dauben, W.G.; Salem, L.; Turro, N.J. *Acc. Chem. Res.* ***1975***, *8*, 41. For reviews of photochemical reactions where the molecules are geometrically constrained, see Ramamurthy, V. *Tetrahedron* ***1986***, *42*, 5753; Ramamurthy, V.; Eaton, D.F. *Acc. Chem. Res.* ***1988***, *21*, 300; Turro, N.J.; Cox, G.S.; Paczkowski, M.A. *Top. Curr. Chem.* ***1985***, *129*, 57.

[40] Turro, N.J.; Lechtken, P.; Lyons, A.; Hautala, R.T.; Carnahan, E.; Katz, T.J. *J. Am. Chem. Soc.* ***1973***, ***95***, 2035.

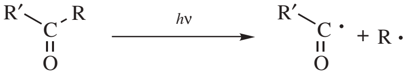
[41] For monographs on the use of photochemistry for synthesis, see Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***; Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***; Schönberg, A. *Preparative Organic Photochemistry*, Springer, Berlin, ***1968***.

TABLE 7.5. Primary photochemical reactions[a] of an excited molecule A—B—C[38]

Reaction	Reaction Type	Example Number
$(A{-}B{-}C) \longrightarrow A{-}B\bullet + C\bullet$	Simple cleavage into radicals[42]	(1)
$(A{-}B{-}C) \longrightarrow E + F$	Decomposition into molecules	(2)
$(A{-}B{-}C) \longrightarrow A{-}C{-}B$	Intramolecular rearrangement	(3)
$(A{-}B{-}C) \longrightarrow A{-}B{-}C'$	Photoisomerization	(4)
$(A{-}B{-}C) \xrightarrow{RH} A{-}B{-}C{-}H + R\bullet$	Hydrogen-atom abstraction	(5)
$(A{-}B{-}C) \longrightarrow (ABD)_2$	Photodimerization	(6)
$(A{-}B{-}C) \xrightarrow{A} ABC + A^*$	Photosensitization	(7)

[a] Examples are given in the text; the most common are (1), (2), and, in the presence of a suitable acceptor molecule, (7).

Category 1. *Simple Cleavage into Radicals.*[43] Aldehydes and ketones absorb in the 230–330-nm region. This is assumed to result from an $n \rightarrow \pi^*$ singlet–singlet transition. The excited aldehyde or ketone can then cleave.[44]



When applied to ketones, this is called *Norrish Type I cleavage* or often just *Type I cleavage*. In a secondary process, the acyl radical R′—CO• can then lose CO to give R′• radicals. Another example of a category 1 process is cleavage of Cl_2 to give two Cl atoms. Other bonds that are easily cleaved by photolysis are the O—O bonds of peroxy compounds and the C—N bonds of aliphatic azo

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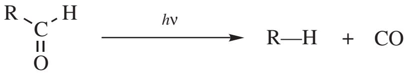
[42] For a polymer-supported reagent used for the photochemical generation of radicals in solution see DeLuca, L.; Giacomelli, G.; Porcu, G.; Taddei, M. *Org. Lett.* ***2001***, *3*, 855.

[43] For reviews, see Jackson, W.M.; Okabe, H. *Adv. Photochem.* ***1986***, *13*, 1; Kresin, V.Z.; Lester Jr., W.A. *Adv. Photochem.* ***1986***, *13*, 95.

[44] For full discussions of aldehyde and ketone photochemistry, see Formosinho, S.J.; Arnaut, L.G. *Adv. Photochem.* ***1991***, *16*, 67; Newton, R.F., in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 39–60; Lee, E.K.C.; Lewis, R.S. *Adv. Photochem.* ***1980***, *12*, 1; Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, pp. 368–427; Coyle, J.D.; Carless, H.A. J. *Chem. Soc. Rev.* ***1972***, *1*, 465; Pitts, Jr., J.N.; Wan, J.K.S., in Patai, S. *The Chemistry of the Carbonyl Group*, Wiley, NY, ***1966***, pp. 823–916; Dalton, J.C.; Turro, N.J. *Annu. Rev. Phys. Chem.* ***1970***, *21*, 499; Bérces, T. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5; Elsevier, NY, ***1972***, pp. 277–380; Turro, N.J.; Dalton, J.C.; Dawes, K.; Farrington, G.; Hautala, R.; Morton, D.; Niemczyk, M.; Shore, N. *Acc. Chem. Res.* ***1972***, *5*, 92; Wagner, P.J. *Top. Curr. Chem.* ***1976***, *66*, 1; Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21, 87–129. For reviews of the photochemistry of cyclic ketones, see Weiss, D.S. *Org. Photochem.* ***1981***, *5*, 347; Chapman, O.L.; Weiss, D.S. *Org. Photochem.* ***1973***, *3*, 197; Morton, B.M.; Turro, N.J. *Adv. Photochem.* ***1974***, *9*, 197. For reviews of the photochemistry of α-diketones, see Rubin, M.B. *Top. Curr. Chem.* ***1985***, *129*, 1; ***1969***, *13*, 251; Monroe, B.M. *Adv. Photochem.* ***1971***, *8*, 77. For a review of the photochemistry of protonated unsaturated carbonyl compounds, see Childs, R.F. *Rev. Chem. Intermed.* ***1980***, *3*, 285. For reviews of the photochemistry of C=S compounds, see Coyle, J.D. *Tetrahedron* ***1985***, *41*, 5393; Ramamurthy, V. *Org. Photochem.* ***1985***, *7*, 231. For a review of the chemistry of C=N compounds, see Mariano, P.S. *Org. Photochem.* ***1987***, *9*, 1.

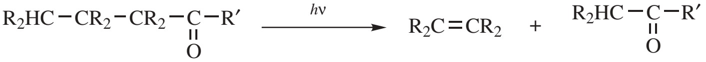
compounds R—N=N—R.[45] The latter is an important source of radicals R•, since the other product is the very stable N_2.

Category 2. *Decomposition into Molecules*. Aldehydes (though not generally ketones) can also cleave in this manner:



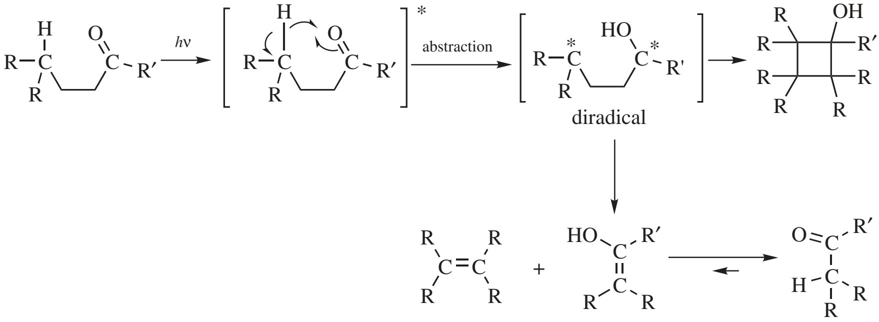
$$\mathrm{R{-}C({=}O){-}H} \xrightarrow{h\nu} \mathrm{R{-}H} + \mathrm{CO}$$

This is an extrusion reaction (see Chapter 17). In another example of a process in category 2, aldehydes and ketones with a γ hydrogen can cleave in still another way (a β elimination, see Chapter 17):



$$\mathrm{R_2HC{-}CR_2{-}CR_2{-}C({=}O){-}R'} \xrightarrow{h\nu} \mathrm{R_2C{=}CR_2} + \mathrm{R_2HC{-}C({=}O){-}R'}$$

This reaction, called *Norrish Type II cleavage*,[46] involves intramolecular abstraction of the γ hydrogen followed by cleavage of the resulting diradical[47] (a secondary reaction) to give an enol that tautomerizes to the aldehyde or ketone product.[48]



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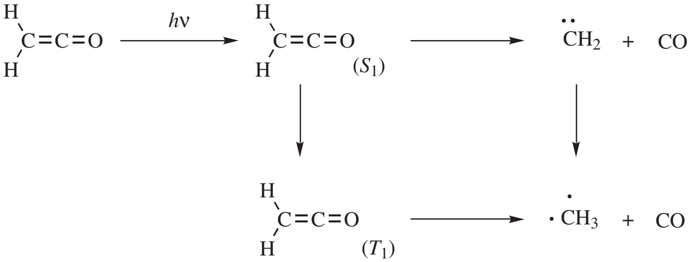
[45] For reviews of the photochemistry of azo compounds, see Adam, W.; Oppenländer, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 661; Dürr, H.; Ruge, B. *Top. Curr. Chem.* ***1976***, *66*, 53; Drewer, R.J., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 935–1015.

[46] For thorough discussions of the mechanism, see Wagner, P.J., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 381–444; *Acc. Chem. Res.* ***1971***, *4*, 168; Dalton, J.C.; Turro, N.J. *Annu. Rev. Phys. Chem.* ***1970***, *21*, 499, 526–538. See Niu, Y.; Christophy, E.; Hossenlopp, J.M. *J. Am. Chem. Soc.* ***1996***, *118*, 4188 for a new view of Norrish Type II elimination.

[47] For reviews of the diradicals produced in this reaction, see Wilson, R.M. *Org. Photochem.* ***1985***, *7*, 339, 349–373; Scaiano, J.C.; Lissi, E.A.; Encina, M.V. *Rev. Chem. Intermed.* ***1978***, *2*, 139. For a review of a similar process, where δ hydrogens are abstracted, see Wagner, P.J. *Acc. Chem. Res.* ***1989***, *22*, 83.

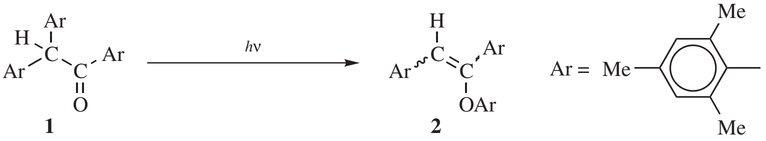
[48] This mechanism was proposed by Yang, N.C.; Yang, D.H. *J. Am. Chem. Soc.* ***1958***, *80*, 2913. Among the evidence for this mechanism is the fact that the diradical intermediate has been trapped: Wagner, P.J.; Zepp, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 287; Wagner, P.J.; Kelso, P.A.; Zepp, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 7480; Adam, W.; Grabowski, S.; Wilson, R.M. *Chem. Ber.* ***1989***, *122*, 561. See also Caldwell, R.A.; Dhawan, S.N.; Moore, D.E. *J. Am. Chem. Soc.* ***1985***, *107*, 5163.

Both singlet and triplet n,π^* states undergo the reaction.[49] The intermediate diradical can also cyclize to a cyclobutanol, which is often a side product. Carboxylic esters, anhydrides, and other carbonyl compounds can also give this reaction.[50] The photolysis of ketene to CH_2 (p. 288) is still another example of a reaction in category 2. Both singlet and triplet CH_2 are generated, the latter in two ways:

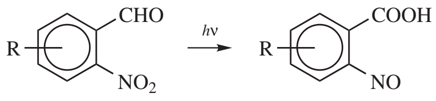


Reactions are known where *both* Norrish Type I and Norrish Type II reactions compete, and the substituents on and nature of the substrate will determine which leads to the major product.[51]

Category 3. *Intramolecular Rearrangement*. Two examples are the rearrangement of the trimesityl compound (**1**) to the enol ether (**2**),[52] and irradiation of *o*-nitrobenzaldehydes (**3**) to give *o*-nitrosobenzoic acids (**4**).[53]



1 **2**



3 **4**

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[49] Wagner, P.J.; Hammond, G.S. *J. Am. Chem. Soc.* ***1965***, *87*, 4009; Dougherty, T.J. *J. Am. Chem. Soc.* ***1965***, *87*, 4011; Ausloos, P.; Rebbert, R.E. *J. Am. Chem. Soc.* ***1964***, *86*, 4512; Casey, C.P.; Boggs, R.A. *J. Am. Chem. Soc.* ***1972***, *94*, 6457.

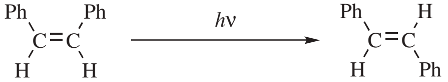
[50] For a review of the photochemistry of carboxylic acids and acid derivatives, see Givens, R.S.; Levi, N., in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 641–753.

[51] See Hwu, J.R.; Chen, B.-L.; Huang, L.W.; Yang, T.-H. *J. Chem. Soc. Chem. Commun.* ***1995***, 299 for an example.

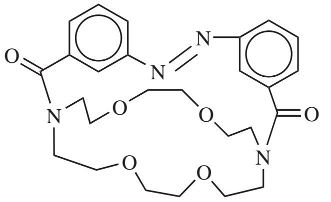
[52] Hart, H.; Lin, L.W. *Tetrahedron Lett.* ***1985***, *26*, 575; Wagner, P.J.; Zhou, B. *J. Am. Chem. Soc.* ***1988***, *110*, 611.

[53] For a review of this and closely related reactions, see Morrison, H.A., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1; Wiley, NY, ***1969***, pp. 165–213, 185–191. For a review of photochemical rearrangements of benzene derivatives, see Kaupp, G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 243. See also, Yip, R.W.; Sharma, D.K. *Res. Chem. Intermed.* ***1989***, *11*, 109.

Category 4. *Photoisomerization*. The most common reaction in this category is photochemical cis–trans isomerization.[54] For example, *cis*-stilbene can be converted to the trans isomer,[55] and the photoisomerization of *O*-methyl oximes is known.[56]



The isomerization takes place because the excited states, both S_1 and T_1, of many alkenes have a perpendicular instead of a planar geometry (p. 334), so cis–trans isomerism disappears upon excitation. When the excited molecule drops back to the S_0 state, either isomer can be formed. A useful example is the photochemical conversion of *cis*-cyclooctene to the much less stable trans isomer.[57] Another interesting example of this isomerization involves azo crown ethers. The crown ether **5**, in which the N=N bond is anti, preferentially binds NH_4^+, Li^+, and Na^+, but the syn isomer preferentially binds K^+ and Rb^+ (see p. 119). Thus, ions can be selectively put in or taken out of solution merely by turning a light source on or off.[58]



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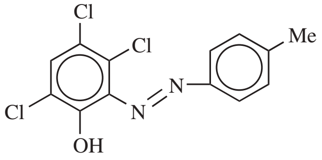

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In another example, the trans azo compound **6** is converted to its cis isomer when exposed to light. In this case[59] the cis isomer is a stronger acid than the

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[54] For reviews of cis–trans isomerizations, see Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557; Schulte-Frohlinde, D.; Görner, H. *Pure Appl. Chem.* ***1979***, *51*, 279; Saltiel, J.; Charlton, J.L., in de Mayo, P. *Rearrangements in Grund and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 25–89; Saltiel, J.; Chang, D.W.L.; Megarity, E.D.; Rousseau, A.D.; Shannon, P.T.; Thomas, B.; Uriarte, A.K. *Pure Appl. Chem.* ***1975***, *41*, 559; Saltiel, J.; D'Agostino, J.; Megarity, E.D.; Metts, L.; Neuberger, K.R.; Wrighton, M.; Zafiriou, O.C. *Org. Photochem.* ***1979***, *3*, 1. For reviews of the photochemistry of alkenes, see Leigh, W.J.; Srinivasan, R. *Acc. Chem. Res.* ***1987***, *20*, 107; Steinmetz, M.G. *Org. Photochem.* ***1987***, *8*, 67; Adam, W.; Oppenländer, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 661; Mattes, S.L.; Farid, S. *Org. Photochem.* ***1984***, *6*, 233; Kropp, P.J. *Org. Photochem.* ***1979***, *4*, 1; Morrison, H. *Org. Photochem.* ***1979***, *4*, 143; Kaupp, G. *Angew. Chem. Int. Ed.* ***1978***, *17*, 150. For a review of the photochemistry of allenes and cumulenes, see Johnson, R.P. *Org. Photochem.* ***1985***, *7*, 75.

[55] For a review of the photoisomerization of stilbenes, see Waldeck, D.H. *Chem. Rev.* ***1991***, *91*, 415.

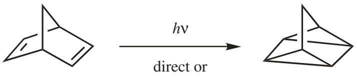
[56] Kawamura, Y.; Takayama, R.; Nishiuchi, M.; Tsukayama, M. *Tetrahedron Lett.* ***2000***, *41*, 8101.

[57] Deyrup, J.A.; Betkouski, M. *J. Org. Chem.* ***1972***, *37*, 3561.

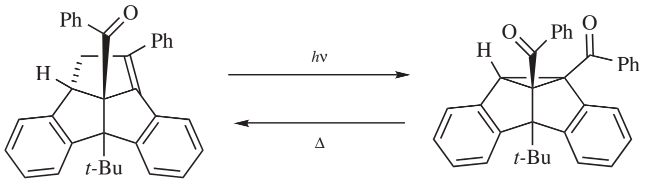
[58] Shinkai, S.; Nakaji, T.; Nishida, Y.; Ogawa, T.; Manabe, O. *J. Am. Chem. Soc.* ***1980***, *102*, 5860. See also, Irie, M.; Kato, M. *J. Am. Chem. Soc.* ***1985***, *107*, 1024; Akabori, S.; Kumagai, T.; Habata, Y.; Sato, S. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1497; Shinkai, S.; Yoshioka, A.; Nakayama, H.; Manabe, O. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1905. For a review, see Shinkai, S.; Manabe, O. *Top. Curr. Chem.* ***1984***, *121*, 67.

[59] Haberfield, P. *J. Am. Chem. Soc.* ***1987***, *109*, 6177.

trans. The trans isomer is dissolved in a system containing a base, wherein a liquid membrane separates two sides, one of which is illuminated, the other kept dark. On the illuminated side, the light converts the trans isomer to the cis. The cis isomer, being a stronger acid, donates its proton to the base, converting *cis*-ArOH to *cis*-ArO$^-$. This ion migrates to the dark side, where it rapidly reverts to the *trans* ion, which reacquires a proton. Because each cycle forms one H_3O^+ ion in the illuminated compartment and one ^-OH ion in the dark compartment, the process reverses the normal reaction whereby these ions neutralize each other.[60] Thus the energy of light is used to do chemical work.[61] Another example of a category 4 reaction is the conversion of bicyclo[2.2.1]hept-2,5-diene to **7**.[54] The thermal isomerization of dibenzosemibullvalene **9** to the corresponding dibenzodihydropentalenofuran **8** in quantitative yield was known,[62] but in another example of a category 4 reaction the photochemical isomerization of **8** to **9** has now been reported.[63]



7



8 **9**

These examples illustrate that the use of photochemical reactions can make it very easy to obtain compounds that would be difficult to get in other ways. Reactions similar to these are discussed at **15-63**.

Category 5. *Hydrogen-Atom Abstraction*. When benzophenone is irradiated in isopropyl alcohol, the initially formed S_1 state crosses to the T_1 state, which abstracts hydrogen from the solvent to give the radical **10**. Radical **10** then

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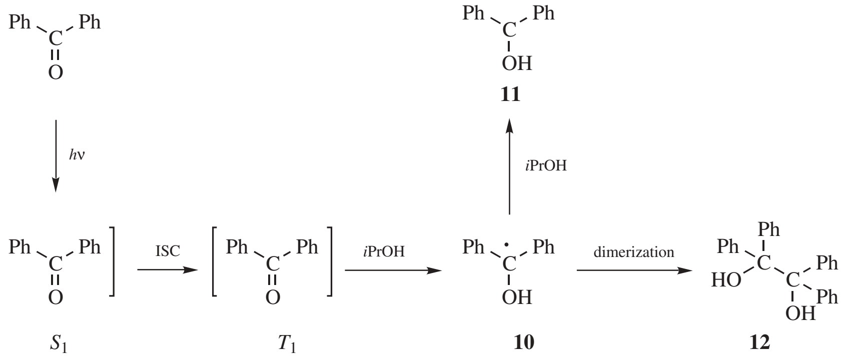
[60] Haberfield, P. *J. Am. Chem. Soc.* ***1987***, *109*, 6178.

[61] For a review of instances where macrocycles change in response to changes in light, pH, temperature, and so on, see Beer, P.D. *Chem. Soc. Rev.* ***1989***, *18*, 409. For an example not involving a macrocycle, see Feringa, B.L.; Jager, W.F.; de Lange, B.; Meijer, E.W. *J. Am. Chem. Soc.* ***1991***, *113*, 5468.

[62] Sajimon, M.C.; Ramaiah, D.; Muneer, M.; Ajithkumar, E.S.; Rath, N.P.; George, M.V. *J. Org. Chem.* ***1999***, *64*, 6347; Sajimon, M.C.; Ramaiah, D.; Muneer, M.; Rath, N.P.; George, M.V. *J. Photochem. Photobiol. A Chem.* **2000**, *136*, 209.

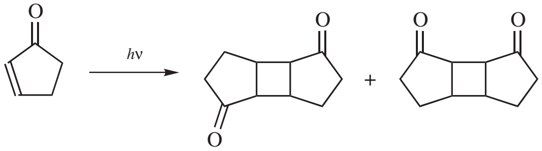
[63] Sajimon, M.C.; Ramaiah, D.; Thomas, K.G.; George, M.V. *J. Org. Chem.* ***2001***, *66*, 3182.

abstracts another hydrogen to give benzhydrol (**11**) or dimerizes to benzpinacol (**12**):



An example of intramolecular abstraction has already been given (p. $$$).

Category 6. *Photodimerization.* An example is dimerization of cyclopentenone:[64]



See reaction **15-63** for a discussion of this and similar reactions.

The Determination of Photochemical Mechanisms[65]

The methods used for the determination of photochemical mechanisms are largely the same as those used for organic mechanisms in general (Chapter 6): product identification, isotopic tracing, the detection and trapping of intermediates, and kinetics. There are, however, a few new factors: (*1*) there are generally many products in a photochemical reaction, as many as 10 or 15; (*2*) in measuring kinetics, there are more variables, since we can study the effect on the rate of the intensity or the wavelength of light; (*3*) in the detection of intermediates by spectra we can use the technique of *flash photolysis*, which can detect extremely short-lived intermediates.

In addition to these methods, there are two additional techniques.

1. The use of emission (fluorescence and phosphorescence) as well as absorption spectroscopy. From these spectra the presence of as well as the energy and lifetime of singlet and triplet excited states can often be calculated.

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[64] Eaton, P.E. *J. Am. Chem. Soc.* ***1962***, *84*, 2344, 2454, *Acc. Chem. Res.* ***1968***, *1*, 50. For a review of the photochemistry of α,β-unsaturated ketones, see Schuster, D.I., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 623–756.

[65] For a review, see Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, pp. 580–670.

2. The study of quantum yields. The *quantum yield* is the fraction of absorbed light that goes to produce a particular result. There are several types. A *primary quantum yield* for a particular process is the fraction of molecules absorbing light that undergo that particular process. Thus, if 10% of all the molecules that are excited to the S_1 state cross over to the T_1 state, the primary quantum yield for that process is 0.10. However, primary quantum yields are often difficult to measure. A *product quantum yield* (usually designated Φ) for a product P that is formed from a photoreaction of an initially excited molecule A can be expressed as

$$\Phi = \frac{\text{number of molecules of P formed}}{\text{number of quanta absorbed by A}}$$

Product quantum yields are much easier to measure. The number of quanta absorbed can be determined by an instrument called an *actinometer*, which is actually a standard photochemical system whose quantum yield is known. An example of the information that can be learned from quantum yields is the following. If the quantum yield of a product is finite and invariant with changes in experimental conditions, it is likely that the product is formed in a primary rate-determining process. Another example: in some reactions, the product quantum yields are found to be well over 1 (perhaps as high as 1000). Such a finding indicates a chain reaction (see p. $$$ for a discussion of chain reactions).

SONOCHEMISTRY

Sonochemistry (chemical events induced by exposure to ultrasound) occupies an important place in organic chemistry.[66] The chemical effects of high-intensity ultrasound were extensively studied in aqueous solutions for many years,[67] but is now applied to a variety of organic solvents. The origin of sonochemistry is acoustic cavitation: the creation, growth, and implosive collapse of gas vacuoles in solution by the sound field. Acoustic cavitation is the phenomenon by which intense ultrasonic waves induce the formation, oscillation, and implosion of gas

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[66] Mason, T.J., Ed. *Advances in Sonochemistry*; JAI Press, NY, ***1990-1994***; Vols. 1–3; Price, G.J., Ed. *Current Trends in Sonochemistry*, Royal Society of Chemistry, Cambridge, UK, ***1992***; Suslick, K.S. *Science* ***1990***, *247*, 1439; Suslick, K.S. *Ultrasound: Its Chemical, Physical, and Biological Effects*, VCH, NY, ***1988***; Knapp, R.T.; Daily, J.W.; Hammitt, F.G. *Cavitation*, McGraw-Hill, NY, ***1970***; Young, F.R. *Cavitation*, McGraw-Hill, NY, ***1989***; Brennen, C.E. *Cavitation and Bubble Dynamics*, Oxford University Press, Oxford, UK, ***1995***; Anbar, M. *Science* ***1968***, *161*, 1343.

[67] Apfel, R.E., in Edmonds, P. *Methods in Experimental Physics*, Academic Press: New York, ***1981***; Vol. 19; Margulis, M.A. *Russ. J. Phys. Chem.* ***1976***, *50*, 1; Chendke, P.K.; Fogler, H.S. *Chem. Eng. J.* ***1974***, *8*, 165; Makino, K.; Mossoba, M.M.; Riesz, P. *J. Am. Chem. Soc.* ***1982***, *104*, 3537.

bubbles in liquids.[68] Liquids irradiated with high-power ultrasound undergo chemical decomposition and emit light.[69] These phenomena occur near the end of the collapse of bubbles expanded many times their equilibrium sizes. Chemistry (sonochemistry), light emission (sonoluminescence), and cavitation noise often accompany the process of acoustic cavitation.[70]

The collapse of gas vaculoes generates transient hot spots with local temperatures and pressures of several thousand degree K and hundreds of atmosphere. A sonochemical hot spot forms where the gas- and liquid-phase reaction zones have effective temperatures of 5200 and 1900 K, respectively.[71] The high temperatures and pressures that are achieved in the bubbles during the quasiadiabatic collapse[72] lead to the generation of chemistry and to the emission of light, most probably coming from molecular excited states and molecular recombination results. Note that work has been done that shows the commonly held view that bubbles are filled with saturated gas is inconsistent with a realistic estimate of condensation rates.[73] The alternative view of extensive solvent vapor supersaturation in bubbles uniformly heated to a few thousand K, depending on the conditions, is in accord with sonochemical rates and products.[74]

There is a correlation between sonochemical and sonoluminescence measurements, which is usually not observed. Sonoluminescence is the consequence that both the sonochemical production (under air) of oxidizing species and the emission of light reflect the variations of the primary sonochemical acts, which are themselves due to variations of the number of "active" bubbles.[75] Pulsed ultrasound in the high-frequency range (>1 MHz) is extensively used in medical diagnosis, and the effects of pulsed ultrasound in the 20-kHz range using an immersed titanium horn has been reported.[76]

The chemical effects of ultrasound have been studied for >50 years,[77] and applied to colloid chemistry in the 1940s.[78] Modern interest in the chemical uses

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[68] Stottlemeyer, T.R.; Apfel, R.E. *J. Acoust. Soc. Am.* ***1997***, *102*, 1413.

[69] Suslick, K.S.; Crum, L.A., in *Sonochemistry and Sonoluminescence, Handbook of Acoustics*; Crocker, M.J., Ed., Wiley, NY, ***1998***, Chapt. 23; Leighton, T.G. *The Acoustic Bubble*, Academic Press, London, ***1994***, Chapter 4, Brennen, C.E. *Cavitation and Bubble Dynamics*, Oxford University Press, ***1995***; Chapts. 1–4. (4) Hua, I.; Hoffmann, M.R. *Environ. Sci. Technol.* ***1997***, *31*, 2237.

[70] Suslick, K.S.; Didenko, Y.T.; Fang, M.M.; Hyeon, T.; Kolbeck, K.J.; McNamara, III, W.B.; Mdleleni, M.M.; Wong, M. *Philos. Trans. R. Soc. London A* ***1999***, *357*, 335. For problems of sonochemistry and cavitation, see Margulis, M.A. *Ultrasonics Sonochemistry*, ***1994***, *1*, S87.

[71] Suslick, K.S.; Hammerton, D.A.; Cline Jr., R.E. *J. Am. Chem. Soc.* ***1986***, *108*, 5641.

[72] Didenko, Y.T.; McNamara III, W.B.; Suslick, K.S. *J. Am. Chem. Soc.* ***1999***, *121*, 5817.

[73] Colussi, A. J.; Hoffmann, M.R. *J. Phys. Chem. A.* ***1999***, *103*, 11336.

[74] Colussi, A.J.; Weavers, L.K.; Hoffmann, M.R. *J. Phys. Chem. A* ***1998***, *102*, 6927; Hart, E.J.; Henglein, A. *J. Phys. Chem.* ***1985***, *89*, 4342.

[75] Segebarth, N.; Eulaerts, O.; Reisse, J.; Crum, L. A.; Matula, T. J. *J. Phys. Chem. B.* ***2002***, *106*, 9181.

[76] Dekerckheer, C.; Bartik, K.; Lecomte, J.-P.; Reisse, J. *J. Phys. Chem. A.* ***1998***, *102*, 9177.

[77] Elpiner, I. E. *Ultrasound: Physical, Chemical, and Biological Effects*, Consultants Bureau, NY, ***1964***.

[78] Sollner, K. *Chem. Rev.* ***1944***, *34*, 371.

of ultrasound involve chemistry in both homogeneous[79] and heterogeneous[80] systems. Organic solvents, such as alkanes, support acoustic cavitation and the associated sonochemistry, and this leads to carbon–carbon bond cleavage and radical rearrangements, with the peak temperatures reached in such cavities controlled by the vapor pressure of the solvent.[81]

It is often difficult to compare the sonochemical results reported from different laboratories (the reproducibility problem in sonochemistry).[82] The sonochemical power irradiated into the reaction system can be different for different instruments. Several methods are available to estimate the amount of ultrasonic power entered into a sonochemical reaction,[82] the most common being calorimetry. This experiment involves measurement of the initial rate of a temperature rise produced when a system is irradiated by power ultrasound. It has been shown that calorimetric methods combined with the Weissler reaction can be used to standardize the ultrasonic power of individual ultrasonic devices.[83]

Sonochemistry has been used to facilitate or assist many organic reactions,[84] as well as other applications.[85] The scope of reactions studied is beyond this work, but some representative examples will be listed. Ultrasound has been used to promote lithiation of organic compounds,[86] for the generation of carbenes,[87] and

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[79] Suslick, K.S.; Schubert, P.F.; Goodale, J.W. *J. Am. Chem. Soc.* ***1981***, *103*, 7342; Lorimer, J.P.; Mason, T.J. *J. Chem. Soc., Chem. Commun.* ***1980***,1135; Margulis, M.A. *Khim. Zh.* ***1981***, 57; Nishikawa, S.; Obi, U.; Mashima, M. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 1716; Yu, T.J.; Sutherland, R.G.; Verrall, R.E. *Can. J. Chem.* ***1980***, *58*, 1909; Sehgal, C.; Sutherland, R.G.; Verrall, R.E. *J. Phys. Chem.* ***1980***, *84*, 2920; Sehgal, C.; Yu, T.J.; Sutherland, R.G.; Verrall, R.E. *J. Phys. Chem.* ***1982***, *86*,2982; Sehgal, C.M.; Wang, S.Y. *J. Am. Chem. Soc.* ***1981***, *103*, 6606; Staas, W.H.; Spurlock, L.A. *J. Chem. Soc., Perkin Trans. I* ***1975***, 1675.

[80] Han, B.-H.; Boudjouk, P. *J. Org. Chem.* ***1982***, *47*, 5030; Boudjouk, P.; Han, B.-H. *Tetrahedron Lett.* ***1981***, *22*, 3813; Han, B.-H.; Boudjouk, P. *J. Org. Chem.* ***1982***, *47*, 751; Boudjouk, P.; Han, B.-H.; Anderson, K.R. *J. Am. Chem. Soc.* ***1982***, *104*, 4992; Boudjouk, P.; Han, B.-H. *J. Catal.* ***1983***, *79*, 489; Fry, A.J.; Ginsburg, G.S. *J. Am. Chem. Soc.* ***1979***, *101*, 3927; Kitazume, T.; Ishikawa, N. *Chem. Lett.* ***1981***, 1679; Kristol, D.S.; Klotz, H.; Parker, R.C. *Tetrahedron Lett.* ***1981***, *22*, 907; Lintner, W.; Hanesian, D. *Ultrasonics* ***1977***, *15*, 21; Luche, J.-L.; Damiano, J. *J. Am. Chem. Soc.* ***1980***, *102*, 7926; Moon, S.; Duchin, L.; Cooney, J.V. *Tetrahedron Lett.* ***1979***, 3917; Racher, S.; Klein, P. *J. Org. Chem.* ***1981***, *46*, 3558; Regen, S.L.; Singh, A. *J. Org. Chem.* ***1982***, *47*, 1587; Kegelaers, Y.; Eulaerts, O.; Reisse, J.; Segebarth, N. *Eur. J. Org. Chem.* ***2001***, 3683.

[81] Suslick, K.S. Gawienowski, J.J.; Schubert, P.F.; Wang, H.H. *J. Phys. Chem.* ***1983***, *87*, 2299.

[82] Mason, T.J. *Practical Sonochemistry: User's Guide to Applications in Chemistry and Chemical Engineering*, Ellis Horwood, West Sussex, ***1991***, pp. 43–46; Broeckaert, L.; Caulier, T.; Fabre, O.; Maerschalk, C.; Reisse, J.; Vandercammen, J.; Yang, D.H.; Lepoint, T.; Mullie, F. *Current Trends in Sonochemistry*, Price, G.J., Ed., Royal Society of Chemistry, Cambridge, ***1992***, p. 8; Mason, T.J.; Lorimer, J.P.; Bates, D.M.; Zhao, Y. *Ultrasonics Sonochemistry* ***1994***, *1*, S91; Mason, T.J.; Lorimer, J.P.; Bates, D.M. *Ultrasonics* ***1992***, *30*, 40.

[83] Kimura, T.; Sakamoto, T.; Leveque, J.-M.; Sohmiya, H.; Fujita, M.; Ikeda, S.; Ando, T. *Ultrasonics Sonochemistry* ***1996***, *3*, S157.

[84] *Synthetic Organic Sonochemistry*, Luche, J.-L. (Universite de Savoie, France), Plenum Press, NY. ***1998***; Luche, J.-L. *Ultrasonics Sonochemistry* ***1996***, *3*, S215; Bremner, D.H. *Ultrasonics Sonochemistry* ***1994***, *1*, S119.

[85] Thompson, L.H.; Doraiswamy, L.K. *Ind. Eng. Chem. Res.* ***1999***, *38*, 1215; Adewuyi, Y.G. *Ind. Eng. Chem. Res.* ***2001***, *40*, 4681.

[86] Boudjouk, P.; Sooriyakumaran, R.; Han, B.H. *J. Org. Chem.* ***1986***, *51*, 2818, and Ref. 1 therein.

[87] Regen, S.L.; Singh, A. *J. Org. Chem.* ***1982***, *47*, 1587.

reactions of metal carbonyls where sonochemical ligand dissociation has been observed, which often produces multiple CO substitution.[88] The influence of ultrasound on phase-transfer catalyzed thioether synthesis has been studied.[89]

Sonochemistry has been applied to acceleration of the Reformatsky reaction,[90] Diels–Alder reactions,[91] the arylation of active methylene compounds[92] nucleophilic aromatic substitution of haloarenes,[93] and to hydrostannation and tin hydride reduction.[94] Other sonochemical applications involve the reaction of benzyl chloride and nitrobenzene,[95] a $S_{RN}1$ reaction in liquid ammonia at room temperature,[96] and Knoevenagel condensation of aromatic aldehydes.[97] Iodination of aliphatic hydrocarbons can be accelerated,[98] and oxyallyl cations have been prepared from α,α'-diiodoketones using sonochemistry.[99] Sonochemistry has been applied to the preparation of carbohydrate compounds.[100] When sonochemistry is an important feature of a chemical reaction, this fact will be noted in the reactions presented in Chapters 10–19.

MICROWAVE CHEMISTRY

In 1986, independent work by Gedye and co-workers[101] as well as Giguere and Majetich[102] reported the advantages of microwave irradiation for organic synthesis. Gedye described four different types of reactions were studied, including the hydrolysis of benzamide to benzoic acid under acidic conditions, and all reactions showed significant rate enhancements when compared to the same reactions done at reflux conditions.[103] Giguere and Majetich reported rate enhancements for microwave-promoted Diels–Alder, Claisen, and ene reactions. At this point,

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[88] Suslick, K.S.; Goodale, J.W.; Schubert, P.F.; Wang, H.H. *J. Am. Chem. Soc.* ***1983***, *105*, 5781.

[89] Wang, M.-L.; Rajendran, V. *J. Mol. Catalysis A: Chemical* ***2005***, *244*, 237.

[90] Han, B.H.; Boudjouk, P. *J. Org. Chem.*, ***1982***, *47*, 5030.

[91] Nebois, P.; Bouaziz, Z.; Fillion, H.; Moeini, L.; Piquer, Ma.J.A.; Luche, J.-L.; Riera, A.; Moyano, A.; Pericàs, M.A. *Ultrasonics Sonochemistry* ***1996***, *3*, 7.

[92] Mečiarová, M.; Kiripolský, M.; Toma, Š *Ultrasonics Sonochemistry* ***2005***, *12*, 401.

[93] Mečiarová, M.; Toma, S.; Magdolen, P. *Ultrasonics Sonochemistry* ***2003***, *10*, 265.

[94] Nakamura, E.; Machii, D.; Inubushi, T. *J. Am. Chem. Soc.* ***1989***, *111*, 6849.

[95] Vinatoru, M.; Stavrescua, R.; Milcoveanu, A.B.; Toma, M.; T.J. Mason, T.J. *Ultrasonics Sonochemistry* ***2002***, *9*, 245.

[96] Manzo, P.G.; Palacios, S.M.; Alonso, R.A. *Tetrahedron Lett.* ***1994***, *35*, 677.

[97] McNulty, J.; Steere, J.A.; Wolf, S. *Tetrahedron Lett.* ***1998***, *39*, 8013.

[98] Kimura, T.; Fujita, M.; Sohmiya, H. Ando, T. *Ultrasonics Sonochemistry* ***2002***, *9*, 205.

[99] Montaña, A.M.; Grima, P.M. *Tetrahedron Lett.* ***2001***, *42*, 7809.

[100] Kardos, N.; Luche, J.-L. *Carbohydrate Res.* ***2001***, *332*, 115.

[101] Gedye R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L. *Tetrahedron Lett.* ***1986***, *27*, 279; Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* ***1987***, *66*, 17.

[102] Giguere, R.J.; Bray, T.; Duncan, S.M.; Majetich, G. *Tetrahedron Lett.* ***1986***, *27*, 4945.

[103] Taken from Horeis, G.; Pichler, S.; Stadler, A.; Gössler, W.; Kappe, C.O. *Microwave-Assisted Organic Synthesis - Back to the Roots*, Fifth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-5), ***2001*** (http://www.mdpi.org/ecsoc-5.htm).

>2000 publications[104] have appeared describing chemical synthesis promoted by microwave irradiation, including many review articles[105] and books.[106]

Microwaves are electromagnetic waves (see p. 329) and there are electric and magnetic field components. Charged particles start to migrate or rotate as the electric field is applied,[107] which leads to further polarization of polar particles. Because the concerted forces applied by the electric and magnetic components of microwaves are rapidly changing in direction (2.4×10^9/s), warming occurs.[107] In general, the most common frequencies used for microwave dielectric heating[108] are 918 MHz and 2.45 GHz[109] (wavelengths of 33.3 and 12.2 cm, respectively), which are in the region between the IR and radiowave wavelengths in the electromagnetic spectrum. For chemical reactions done with microwave irradiation, rapid heating is usually observed, and if a solvent is used superheating of that solvent was always observed.[108] In the early days of microwave chemistry, reactions were often done in open vessels, but also in sealed Teflon or glass vessels using unmodified domestic household ovens.[110] Dielectric heating is direct so if the reaction matrix has a sufficiently large dielectric loss tangent, and contains molecules possessing a dipole moment, a solvent is not required. The use of dry-reaction microwave chemistry is increasingly popular.[111]

Microwave dielectric heating was initially categorized by thermal effects and nonthermal effects.[112] "Thermal effects are those which are caused by the different temperature regime which can be created due to microwave dielectric heating. Nonthermal effects are effects,[113] which are caused by effects specifically inherent to

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[104] Kappe, C. O. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6250.

[105] Majetich, G.; Karen, W. in Kingston, H.M.; Haswell, S.J. *Microwave-Enhanced Chemistry: Fundamentals, Sample Preparation, and Applications*. American Chemical Society, Washington, DC, ***1997***, p 772; Giguere, R.J. *Org. Synth.: Theory Appl.* ***1989***, *1*, 103; Mingos, D.M.P.; Baghurst, D.R. *Chem. Soc. Rev.* ***1991***, *20*, 1; Abramovitch, R.A. *Org. Prep. Proced. Int.* ***1991***, *23*, 683; Bose, A.K.; Manhas, M.S.; Banik, B.K.; Robb, E.W. *Res. Chem. Intermed.* ***1994***, *20*, 1; Majetich, G.; Hicks, R. *Res. Chem. Intermed.* ***1994***, *20*, 61; Strauss, C.R.; Trainor, R.W. *Aust. J. Chem.* ***1995***, *48*, 1665; Caddick, S. *Tetrahedron* ***1995***, *51*, 10403; Mingos, D M.P. *Res. Chem. Intermed.* ***1994***, *20*, 85; Berlan, J. *Rad. Phys. Chem.* ***1995***, *45*, 581; Fini, A.; Breccia, A. *Pure Appl. Chem.* ***1999***, *71*, 573.

[106] Kingston, H. M.; Haswell, S.J. *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation, and Applications*, American Chemical Society, ***1997***; Loupy, A. *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, ***2002***; Hayes, B.L. *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, ***2002***; Lidström, P., Tierney, J.P. *Microwave-Assisted Organic Synthesis*, Blackwell Scientific, ***2005*** ; Kappe, C.O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, ***2005***.

[107] Galema, S.A. *Chem. Soc. Rev.* ***1997***, *26*, 233.

[108] Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* ***1998***, *27*, 213.

[109] This frequencey is usually applied in domestic microwave ovens.

[110] Caddick, S. *Tetrahedron* ***1995***, *51*, 10403.

[111] Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* ***1998***, 1213; Varma, R. S. *Green Chem.* ***1999***, 43; Kidawi, M. *Pure Appl. Chem.* ***2001***, *73*, 147; Varma, R. S. *Pure Appl. Chem.* ***2001***, *73*, 193.

[112] Langa, F.; de la Cruz, P.; de la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* ***1997***, *4*, 373.

[113] See Kuhnert, N. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1863.

the microwaves and are not caused by different temperature regimes."[107] Some claimed special effects[114] in microwave chemistry, such as lowering of Gibbs energy of activation, but later study under careful temperature control indicated no special rate effects.[115] When conventional microwave ovens were used, temperature control was difficult particularly when reactions are carried out in closed reaction vessels. The main contributing factor to any rate acceleration caused by microwave dielectric heating seems to be due to a thermal effect. The thermal effect may be due to a faster initial heating rate or to the occurrence of local regions with higher temperatures.[107]

Conventional microwave ovens are used less often for microwave chemistry today. Microwave reactors for chemical synthesis are commercially available and widely used in academia and in industry. These instruments have built-in magnetic stirring, direct temperature control of the reaction mixture, shielded thermocouples or IR sensors, and the ability to control temperature and pressure by regulating microwave output power.

The applications of microwave chemistry to organic chemistry are too numerous to mention. A few representative examples will be given to illustrate the scope and utility. Microwave chemistry is widely used in synthesis.[116] Examples include the Heck reaction (reaction **13-10**),[117] the Suzuki reaction (reaction **13-12**),[118] the Sonogashira reaction (reaction **13-13**),[119] Ullman type couplings (reaction

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[114] Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* ***1992***, *57*, 7099, and references cited therein.

[115] Raner, K.D.; Strauss, C.R.; Vyskoc, F.; Mokbel, L. J. *Org. Chem.* ***1993***, *58*, 950, and references cited therein.

[116] Abramovitch, R. A. *Org. Prep. Proced. Int.* ***1991***, *23*, 685; Caddick, S. *Tetrahedron* ***1995***, *51*, 10403; Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* ***1995***, *48*, 1665; Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *Chemtech* ***1997***, *27*, 18; Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* ***2001***, *57*, 9225; Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* ***2002***, *35*, 717; Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* ***2004***, *6*, 128; Hayes, B.L. *Aldrichim. Acta* ***2004***, *37*, 66.

[117] Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* ***2002***, *35*, 717; Olofsson, K.; Larhed, M. in Lidström, P.; Tierney, J.P. *Microwave-Assisted Organic Synthesis*, Blackwell, Oxford, ***2004***, Chapt. 2.; Andappan, M.M.S.; Nilsson, P.; Larhed, M. *Mol. Diversity* ***2003***, *7*, 97.

[118] Nuteberg, D.; Schaal, W.; Hamelink, E.; Vrang, L.; Larhed, M. *J. Comb. Chem.* ***2003***, *5*, 456; Miller, S.P.; Morgan, J.B.; Nepveux, F.J.; Morken, J.P. *Org. Lett.* ***2004***, *6*, 131; Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol. Diversity* ***2003***, *7*, 125; Gong, Y.; He, W. *Heterocycles* ***2004***, *62*, 851; Organ, M.G.; Mayer, S.; Lepifre, F.; N'Zemba, B.; Khatri, J. *Mol. Diversity* ***2003***, *7*, 211; Luo, G.; Chen, L.; Pointdexter, G.S. *Tetrahedron Lett.* ***2002***, *43*, 5739; Wu, T.Y.H.; Schultz, P.G.; Ding, S. *Org. Lett.* ***2003***, *5*, 3587; Han, J.W.; Castro, J.C.; Burgess, K. *Tetrahedron Lett.* ***2003***, *44*, 9359; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* ***2003***, *68*, 888; Bai, L.; Wang, J.-X.; Zhang, Y. *Green Chem.* ***2003***, *5*, 615 ; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* ***2003***, *68*, 5660.

[119] Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol. Diversity* ***2003***, *7*, 125; Gong, Y.; He, W. *Heterocycles* ***2004***, *62*, 851; Miljani, O.Š; Vollhardt, K.P.C.; Whitener, G.D. *Synlett* ***2003***, 29; Petricci, E.; Radi, M.; Corelli, F.; Botta, M. *Tetrahedron Lett.* ***2003***, *44*, 9181; Leadbeater, N.E.; Marco, M.; Tominack, B.J. *Org. Lett.* ***2003***, *5*, 3919 ; Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* ***2003***, 4713.

13-3),[120] cycloaddition reactions (reactions **15-58–15-66**),[121] dihydroxylation (reaction **15-48**),[122] and the Mitsunobu reaction (reaction **10-23**).[123] There are a multitude of other reactions types from earlier literature that can be found in the cited review articles. When microwave chemistry is an important feature of a chemical reaction, this fact will be noted in the reactions presented in Chapters 10–19.

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[120] Wu, Y.-J.; He, H.; L'Heureux, A. *Tetrahedron Lett.* ***2003***, *44*, 4217; Lange, J.H.M.; Hofmeyer, L.J.F.; Hout, F.A.S.; Osnabrug, S.J.M.; Verveer, P.C.; Kruse, C.G.; Feenstra, R.W. *Tetrahedron Lett.* ***2002***, *43*, 1101.

[121] For example, see de la Hoz, A.; D'az-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* ***2000***, 3659; Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C.O. *J. Org. Chem.* ***2002***, *67*, 7904 ; Pinto, D.C.G.A.; Silva, A.M.S.; Almeida, L.M.P.M.; Carrillo, J.R.; D'az-Ortiz, A.; de la Hoz, A.; Cavaleiro, J.A.S. *Synlett* ***2003***, 1415.

[122] Dupau, P.; Epple, R.; Thomas, A.A.; Fokin, V.V.; Sharpless, K.B. *Adv. Synth. Catal.* ***2002***, *344*, 421.

[123] Lampariello, L.R.; Piras, D.; Rodriquez, M.; Taddei, M. *J. Org. Chem.* ***2003***, *68*, 7893; Raheem, I.T.; Goodman, S.N.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2004***, *126*, 706.

CHAPTER 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

$$\begin{array}{ccccccc} \text{A—H} & + & \text{B} & \rightleftharpoons & \text{A} & + & \text{B—H} \\ \text{Acid}_1 & & \text{Base}_2 & & \text{Base}_1 & & \text{Acid}_2 \end{array}$$

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

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

[3] According to IUPAC terminology (Bunnett, J.F.; Jones, R.A.Y. *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 ~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.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by
Michael B. Smith and Jerry March

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

$$\mathrm{HCl} + \mathrm{CH_3COO^-} \rightleftharpoons \mathrm{CH_3COOH} + \mathrm{Cl^-}$$

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 (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

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[4] Although equilibrium is reached in most acid–base reactions extremely rapidly (see p. $$$), 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.

[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. 367).

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

[7] Kolthoff, I.M.; Bruckenstein, S., in Kolthoff, I.M.; Elving, P.J. *Treatise on Analytical Chemistry*, Vol. 1, pt. 1; Wiley, NY, ***1959***, pp. 475–542, p. 479.

[8] For reviews of organic compounds protonated at O, N, or S, see Olah, G.A.; White, A.M.; O'Brien, D.H. *Chem. Rev.* ***1970***, *70*, 561; Olah, G.A.; White, A.M.; O'Brien, D.H., in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, Vol. 4; Wiley, NY, ***1973***, pp. 1697–1781.

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.

A crystallographic scale of acidity has been developed, including the acidity of C—H compounds. Measuring the mean C—H•••O distances in crystal structures correlated well with conventional $pK_{a(\text{DMSO})}$ values, where dimethyl sulfoxide = DMSO.[11] An *ab initio* study was able to correlate ring strain in strained hydrocarbons with hydrogen-bond acidity.[12]

The bottom portion of Table 8.1 consists of very weak acids (pK_a above ~17).[13] In most of these acids, the proton is lost from a carbon atom, and such acids are known as *carbon acids*. The 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.[14] The acidity of carbon acids is proportional to the stability of the carbanions that are their conjugate bases (see p. 249).

The extremely strong acids at the top of the table are known as *super acids* (see p. 236).[15] The actual species present in the $FSO_3H—SbF_5$ mixture are probably $H[SbF_5(SO_3F)]$ and $H[SbF_2(SO_3F)_4$.[16] The addition of SO_3 causes formation of the still stronger $H[SbF_4(SO_3F)_2]$, $H[SbF_3(SO_3F)_3]$, and $H[(SbF_5)_2(SO_3F)]$.[16]

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*.[17] It must be emphasized that the order of

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

[10] Rochester, C.H. *Acidity Functions*; Academic Press, NY, ***1970***. For discussion of the basicity of such compounds, see Liler, M. *Reaction Mechanisms in Sulfuric Acid*, Academic Press, NY, ***1971***, pp. 118–139.

[11] Pedireddi, V.R.; Desiraju, G.R. *J. Chem. Soc. Chem. Commun.* ***1992***, 988.

[12] Alkorta, I.; Campillo, N.; Rozas, I.; Elguero, J. *J. Org. Chem.* ***1998***, *63*, 7759.

[13] For a monograph on very weak acids, see Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Pergamon, NY, ***1978***. For other discussions, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 1–45; Streitwieser, Jr., A.; Hammons, J.H. *Prog. Phys. Org. Chem.* ***1965***, *3*, 41. For a study of substituent effects of weak acids see Wiberg, K.B. *J. Org. Chem.* ***2002***, *67*, 1613.

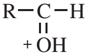
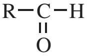
[14] For reviews of methods used to measure the acidity of carbon acids, see Jones, J.R. *Q. Rev. Chem. Soc.* ***1971***, *25*, 365; Fischer, H.; Rewicki, D. *Prog. Org. Chem.* ***1968***, *7*, 116; Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Chapt. 1, Pergamon, NY, ***1978*** [an earlier version of this chapter appeared in *Russ. Chem. Rev.* ***1974***, *43*, 17]; Ref. 6. For reviews on acidities of carbon acids, see Gau, G.; Assadourian, L.; Veracini, S. *Prog. Phys. Org. Chem.* ***1987***, *16*, 237; in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. A, Elsevier, NY, ***1980***, the reviews by Pellerite, M.J.; Brauman, J.I. pp. 55–96 (gas-phase acidities); and Streitwieser, Jr., A.; Juaristi, E.; Nebenzahl, L. pp. 323–381.

[15] For a monograph, see Olah, G.A.; Prakash, G.K.S.; Sommer, J. *Superacids*; Wiley, NY, ***1985***. For a review, see Gillespie, R.J.; Peel, T.E. *Adv. Phys. Org. Chem.* ***1971***, *9*, 1. For a review of solid super acids, see Arata, K. *Adv. Catal.* ***1990***, *37*, 165. For a review of methods of measuring superacidity, see Jost, R.; Sommer, J. *Rev. Chem. Intermed.* ***1988***, *9*, 171.

[16] Gillespie, R.J. *Acc. Chem. Res.* ***1968***, *1*, 202.

[17] 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 ~2 p*K* units).

TABLE 8.1. Thep K_a Values for Many Types of Acids. The values in boldface are exact values; the others are approximate, especially above 18 and below −2.[18]

Acid	Base	Approximate pK_a (relative to water)	References
Super Acids			
$HF{-}SbF_5$	SbF_6^-		19
$FSO_3H{-}SbF_5{-}SO_3$			16
$FSO_3H{-}SbF_5$			16,19
FSO_3H	FSO_3^-		16
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
 $R-\underset{\underset{+OH}{\|}}{C}-H$	 $R-\underset{\underset{O}{\|}}{C}-H$	−10	23
H_2SO_4	HSO_4^-		
HBr	Br^-	−9	21

(*continued*)

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[18] 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 Brown, H.C.; McDaniel, D.H.; Häflinger, O., in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, ***1955***. Values for >5500 organic acids are given, in Serjeant, E.P.; Dempsey, B. *Ionisation Constants of Organic Acids in Aqueous Solution*, Pergamon, Elmsford NY, ***1979***; Kortüm, G.; Vogel, W.; Andrussow, K. *Dissociation Constants of Organic Acids in Aqueous Solution*, Butterworth, London, ***1961***. The index in the 1979 volume covers both volumes. Kortüm, G.; Vogel, W.; Andrussow, K. *Pure Appl. Chem.* ***1960***, *1*, 190 give values for 631 carboxylic acids and 110 phenols. Arnett, E.M. *Prog. Phys. Org. Chem.* ***1963***, *1*, 223 gives hundreds of values for very strong acids (very weak bases). Perrin, D.D. *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworth, London, ***1965***, and Supplement, 1972 list pK values for >7000 amines and other bases. Collumeau, A. *Bull. Soc. Chim. Fr.* ***1968***, 5087 gives pK values for ~800 acids and bases. Bordwell, F.G. *Acc. Chem. Res.* ***1988***, *21*, 456 gives values for >300 acids in dimethyl sulfoxide. For inorganic acids and bases, see Perrin, D.D. *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed., Pergamon, Elmsford NY, ***1982***; *Pure Appl. Chem.* ***1969***, *20*, 133.

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

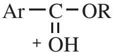
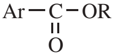
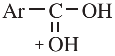
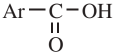
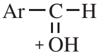
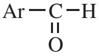
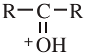
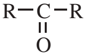
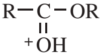
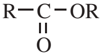
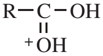
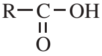
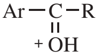
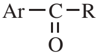
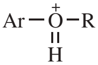
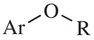
[20] Arnett, E.M. *Prog. Phys. Org. Chem.* ***1963***, *1*, 223, 324–325.

[21] Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***.

[22] Deno, N.C.; Gaugler, R.W.; Wisotsky, M.J. *J. Org. Chem.* ***1966***, *31*, 1967.

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

TABLE 8.1. (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
 $\mathrm{Ar{-}\underset{\underset{{}^{+}OH}{\|}}{C}{-}OR}$[24]	 $\mathrm{Ar{-}\underset{\underset{O}{\|}}{C}{-}OR}$	−7.4	20
HCl	Cl^-	−7	21
RSH_2+	RSH	−7	20
 $\mathrm{Ar{-}\underset{\underset{{}^{+}OH}{\|}}{C}{-}OH}$[24]	 $\mathrm{Ar{-}\underset{\underset{O}{\|}}{C}{-}OH}$	−7	25
 $\mathrm{Ar{-}\underset{\underset{{}^{+}OH}{\|}}{C}{-}H}$	 $\mathrm{Ar{-}\underset{\underset{O}{\|}}{C}{-}H}$	−7	26
 $\mathrm{R{-}\underset{\underset{{}^{+}OH}{\|}}{C}{-}R}$	 $\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}R}$	−7	9,22,27
$ArSO_3H$	$ArSO_3{}^-$	−6.5	28
 $\mathrm{R{-}\underset{\underset{{}^{+}OH}{\|}}{C}{-}OR}$[24]	 $\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}OR}$	−6.5	20
$ArOH_2{}^+$	ArOH	−6.4	29
 $\mathrm{R{-}\underset{\underset{{}^{+}OH}{\|}}{C}{-}OH}$[24]	 $\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}OH}$	−6	20
 $\mathrm{Ar{-}\underset{\underset{{}^{+}OH}{\|}}{C}{-}R}$	 $\mathrm{Ar{-}\underset{\underset{O}{\|}}{C}{-}R}$	−6	26,30
 $\mathrm{Ar{-}\underset{\underset{H}{\|}}{\overset{+}{O}}{-}R}$		−6	29,31
$CH(CN)_3$	$^-C(CN)_3$	−5	32

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[24] 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, A.R.; Jones, R.A.Y. *Chem. Ind. (London)* ***1961***, 722; Ottenheym, J.H.; van Raayen, W.; Smidt, J.; Groenewege, M.P.; Veerkamp, T.A. *Recl. Trav. Chim. Pays-Bas* ***1961***, *80*, 1211; Stewart, R.; Muenster, L.J. *Can. J. Chem.* ***1961***, *39*, 401; Smith, C.R.; Yates, K. *Can. J. Chem.* ***1972***, *50*, 771; Benedetti, E.; Di Blasio, B.; Baine, P. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 500; Ref. 8; Homer, R.B.; Johnson, C.D., in Zabicky, J. *The Chemistry of Amides*; Wiley, NY, ***1970***, pp. 188–197. It has been shown that some amides protonate at nitrogen: see Perrin, C.L. *Acc. Chem. Res.* ***1989***, *22*, 268. For a review of alternative proton sites, see Liler, M. *Adv. Phys. Org. Chem.* ***1975***, *11*, 267.

[25] Stewart, R.; Granger, M.R. *Can. J. Chem.* ***1961***, *39*, 2508.

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[27] Lee, D.G. *Can. J. Chem.* ***1970***, *48*, 1919.

[28] Cerfontain, H.; Koeberg-Telder, A.; Kruk, C. *Tetrahedron Lett.* ***1975***, 3639.

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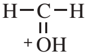
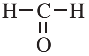
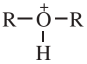
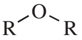
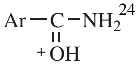
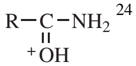
[31] Arnett, E.M.; Wu, C.Y. *J. Am. Chem. Soc.* ***1960***, *82*, 4999.

[32] Boyd, R.H. *J. Phys. Chem.* ***1963***, *67*, 737.

TABLE 8.1. (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
Ar_3NH^+	Ar_3N	−5	33
 $\mathrm{H{-}\underset{\substack{\| \\ {}^{+}OH}}{C}{-}H}$	 $\mathrm{H{-}\underset{\substack{\| \\ O}}{C}{-}H}$	−4	34
 $\mathrm{R{-}\underset{\substack{\mid \\ H}}{\overset{+}{O}}{-}R}$	 $\mathrm{R{-}O{-}R}$	−3.5	22,31,35
$R_3COH_2{}^+$	R_3COH	−2	35
$R_2CHOH_2{}^+$	R_2CHOH	−2	35,36
$RCH_2OH_2{}^+$	RCH_2OH	−2	22,35,36
H_3O^+	H_2O	**−1.74**	37
 $\mathrm{Ar{-}\underset{\substack{\| \\ {}^{+}OH}}{C}{-}NH_2}$[24]	 $\mathrm{Ar{-}\underset{\substack{\| \\ O}}{C}{-}NH_2}$	−1.5	38
HNO_3	$NO_3{}^-$	−1.4	21
 $\mathrm{R{-}\underset{\substack{\| \\ {}^{+}OH}}{C}{-}NH_2}$[24]	 $\mathrm{R{-}\underset{\substack{\| \\ O}}{C}{-}NH_2}$	−0.5	38
$Ar_2NH_2{}^+$	Ar_2NH	1	33
$HSO_4{}^-$	$SO_4{}^{2-}$	**1.99**	39
HF	F^-	**3.17**	39
$HONO$	$NO_2{}^-$	**3.29**	39
$ArNH_3{}^+$	$ArNH_2$	3-5	40
$ArNR_2H^+$	$ArNR_2$	3-5	40
$RCOOH$	$RCOO^-$	4-5	40
$HCOCH_2CHO$	HCOC–HCHO	5	41
H_2CO_3[42]	$HCO_3{}^-$	**6.35**	39
H_2S	HS^-	**7.00**	39
ArSH	ArS^-	6–8	43

(*continued*)

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[37] For a discussion, see Campbell, M.L.; Waite, B.A. *J. Chem. Educ.* ***1990***, *67*, 386.

[38] Cox, R.A.; Druet, L.M.; Klausner, A.E.; Modro, T.A.; Wan, P.; Yates, K. *Can. J. Chem.* ***1981***, *59*, 1568; Grant, H.M.; McTigue, P.; Ward, D.G. *Aust. J. Chem.* ***1983***, *36*, 2211.

[39] Bruckenstein, S.; Kolthoff, I.M., in Kolthoff, I.M.; Elving, P.J. *Treatise on Analytical Chemistry*, Vol. 1, pt. 1; Wiley, NY, ***1959***, pp. 432–433.

[40] Brown, H.C.; McDaniel, D.H.; Häflinger, O., in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1; Academic Press, NY, ***1955***, pp. 567–662.

[41] Pearson, R.G.; Dillon, R.L. *J. Am. Chem. Soc.* ***1953***, *75*, 2439.

[42] This value includes the CO_2 usually present. The value for H_2CO_3 alone is 3.9, in Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***.

[43] Crampton, M.R., in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 396–410.

TABLE 8.1. (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
$CH_3COCH_2COCH_3$[44]	$CH_3COC{-}HCOCH_3$	9	41
HCN	CN^-	9.2	45
NH_4^+	NH_3	**9.24**	39
$ArOH$	ArO^-	8–11	46
RCH_2NO_2	$RC{-}HNO_2$	10	47
R_3NH^+	R_3N	10–11	40
RNH_3^+	RNH_2	10–11	40
HCO_3^-	CO_3^{2-}	**10.33**	39
RSH	RS^-	10–11	43
$R_2NH_2^+$	R_2NH	11	40
$N{\equiv}CCH_2C{\equiv}N$	$N{\equiv}CC{-}HC{\equiv}N$	11	41,48
CH_3COCH_2COOR	$CH_3COC{-}HCOOR$	11	41
$CH_3SO_2CH_2SO_2CH_3$	$CH_3SO_2C{-}HSO_2CH_3$	12.5	49
$EtOOCCH_2COOEt$	$EtOOCC{-}HCOOEt$	13	41
CH_3OH	CH_3O^-	15.2	50,51
H_2O	OH^-	**15.74**	52
		16	53
RCH_2OH	RCH_2O^-	16	50
RCH_2CHO	$RC{-}HCHO$	16	54
R_2CHOH	R_2CHO^-	16.5	50
R_3COH	R_3CO^-	17	50
$RCONH_2$	$RCONH^-$	17	55
$RCOCH_2R$	$RCOC{-}HR$	19-20[56]	57

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[44] See Bunting, J.W.; Kanter, J.P. *J. Am. Chem. Soc.* ***1993***, *115*, 11705 for pK_a values of several β-ketone esters and amides.

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

[46] Rochester, C.H., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, p. 374.

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

[48] Bowden, K.; Stewart, R. *Tetrahedron* ***1965***, *21*, 261.

[49] Hine, J.; Philips, J.C.; Maxwel, J.I. *J. Org. Chem.* ***1970***, *35*, 3943. See also, Ang, K.P.; Lee, T.W.S. *Aust. J. Chem.* ***1977***, *30*, 521.

[50] Reeve, W.; Erikson, C.M.; Aluotto, P.F. *Can. J. Chem.* ***1979***, *57*, 2747.

[51] See also Mackay, G.I.; Bohme, D.K. *J. Am. Chem. Soc.* ***1978***, *100*, 327; Olmstead, W.N.; Margolin, Z.; Bordwell, F.G. *J. Org. Chem.* ***1980***, *45*, 3295.

[52] Harned, H.S.; Robinson, R.A. *Trans. Faraday Soc.* ***1940***, *36*, 973.

[53] Streitwieser Jr., A.; Nebenzahl, L. *J. Am. Chem. Soc.* ***1976***, *98*, 2188.

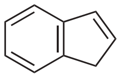
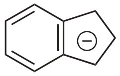
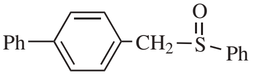
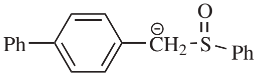
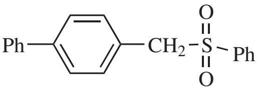
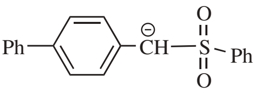
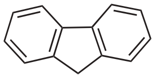
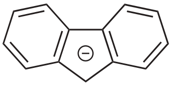
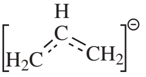
[54] Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1986***, *64*, 2470.

[55] Homer, R.B.; Johnson, C.D., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 238–240.

[56] The pK_a of acetone in DMSO is reported to be 26.5. See Bordwell, F.G.; Zhang, X.-M. *Accts. Chem. Res.* ***1997***, *26*, 510.

[57] Tapuhi, E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1982***, *104*, 5758; Guthrie, J.P.; Cossar, J.; Klym, A. *J. Am. Chem. Soc.* ***1984***, *106*, 1351; Chiang, Y.; Kresge, A.J.; Tang, Y.S.; Wirz, J. *J. Am. Chem. Soc.* ***1984***, *106*, 460.

TABLE 8.1. (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
		20	58,59
		20.08[a]	60
		18.91[a]	60
		23	58,59
$ROOCCH_2R$	ROOCC–HR	24.5	41
$RCH_2C{\equiv}N$	RC–HC=N	25	41,61
$HC{\equiv}CH$	$HC{\equiv}CC^-$	25	62
Ph_2NH	PH_2N^-	24.95[b]	56
$EtOCOCH_3$	$EtOCOCH_2^-$	25.6	63
$PhNH_2$	$PhNH^-$	30.6[b]	56
Ar_3CH	Ar_3C^-	31.5	58,64
Ar_2CH_2	Ar_2CH^-	33.5	58,64
H_2	H^-	35	65
NH_3	NH_2^-	38	66
$PhCH_3$	$PhCH_2^-$	40	67
$CH_2{=}CHCH_3$		43	68
PhH	Ph^-	43	69

[58] Streitwieser, Jr., A.; Ciuffarin, E.; Hammons, J.H. *J. Am. Chem. Soc.* ***1967***, *89*, 63.

[59] Streitwieser, Jr., A.; Hollyhead, W.B.; Pudjaatmaka, H.; Owens, P.H.; Kruger, T.L.; Rubenstein, P.A.; MacQuarrie, R.A.; Brokaw, M.L.; Chu, W.K.C.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1971***, *93*, 5088.

[60] Streitwieser, A.; Wang, G.P.; Bors, D.A. *Tetrahedron* ***1997***, *53*, 10103.

[61] For a review of the acidity of cyano compounds, see Hibbert, F., in Patai, S.; Rappoport, Z. *The Chemistry of Triple-bonded Functional Groups*, pt. 1; Wiley, NY, ***1983***, pp. 699–736.

[62] Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, p. 19. See also, Dessy, R.E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* ***1966***, *88*, 460.

[63] Amyes, T.L.; Richard J.P. *J. Am. Chem. Soc.* ***1996***, *118*, 3129.

[64] Streitwieser, Jr., A.; Hollyhead W.B.; Sonnichsen, G.; Pudjaatmaka, H.; Chang, C.J.; Kruger. T.L. *J. Am. Chem. Soc.* ***1971***, *93*, 5096.

[65] Buncel, E.; Menon, B. *J. Am. Chem. Soc.* ***1977***, *99*, 4457.

[66] Buncel, E.; Menon, B. *J. Organomet. Chem.* ***1977***, *141*, 1.

[67] Streitwieser, Jr., A.; Ni, J.X. *Tetrahedron Lett.* ***1985***, *26*, 6317; Albrech, H.; Schneider, G. *Tetrahedron* ***1986***, *42*, 4729.

[68] Boerth, D.W.; Streitwieser, Jr., A. *J. Am. Chem. Soc.* ***1981***, *103*, 6443.

[69] Streitwieser, Jr., A.; Scannon, P.J.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7936.

TABLE 8.1. (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
$CH_2{=}CH_2$	$CH_2{=}CH^-$	44	70
cyclo-C_3H_6	*c*-$C_3H_5^-$	46	71
CH_4[72]	CH_3^-	48	73
C_2H_6	$C_2H_5^-$	50	74
$(CH_3)_2CH_2$[72]	$(CH_3)_2CH^-$	51	74
$(CH_3)_3CH$[72]	$(CH_3)_3C^-$		75

[a] pK_a in THF.
[b] pK_a in DMSO.

acid strength in Table 8.1 applies 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. 392). In the gas phase, where solvation effects are completely or almost completely absent, acidity orders may also differ greatly.[76] For example, in the gas phase, toluene is a stronger acid than water and *tert*-butoxide ion is a weaker base than methoxide ion[77] (see also, pp. 390–394). It is also possible for the acidity order to change with temperature. For example, >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 <1°C the order becomes Bu_2O > BuOH > H_2O.[78]

A hydrogen-bond basicity scale has been developed that can be used to determine the relative basicity of molecules. Table 8.2 gives the pK_{HB} values for several common heteroatom containing molecules. This is obtained from the protonated form (conjugated acid) of the base in question. The larger the number, the more basic is that compound. The basicity of aliphatic amines has been calculated,[79] the ion-pair

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[70] Streitwieser, Jr., A.; Boerth, D.W. *J. Am. Chem. Soc.* ***1978***, *100*, 755.

[71] This value is calculated from results given in Streitwieser, Jr., A.; Caldwell, R.A.; Young, W.R. *J. Am. Chem. Soc.* ***1969***, *91*, 529. For a review of acidity and basicity of cyclopropanes, see Battiste, M.A.; Coxon, J.M., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley, NY, ***1987***, pp. 255–305.

[72] See Daasbjerg, K. *Acta Chem. Scand. B* ***1995***, *49*, 878 for pK_a values of various hydrocarbons in DMF.

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

[74] These values are based on those given in Cram, D.J. *Chem. Eng. News* ***1963***, *41* (No. 33, Aug. 19), 94, but are corrected to the newer scale of Streitwieser, A.; Streitwieser, Jr., A.; Scannon, P.J.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7936; Streitwieser, Jr., A.; Boerth, D.W. *J. Am. Chem. Soc.* ***1978***, *100*, 755.

[75] Breslow, R. and co-workers report a value of 71 [Breslow, R.; Grant, J.L. *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 ~53. See also Juan, B.; Schwarz, J.; Breslow, R. *J. Am. Chem. Soc.* ***1980***, *102*, 5741.

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

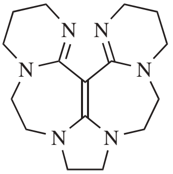
[77] Brauman, J.I.; Blair, L.K. *J. Am. Chem. Soc.* ***1970***, *92*, 5986; Bohme, D.K.; Lee-Ruff, E.; Young, L.B. *J. Am. Chem. Soc.* ***1972***, *94*, 4608, 5153.

[78] Gerrard, W.; Macklen, E.D. *Chem. Rev.* ***1959***, *59*, 1105. For other examples, see Calder, G.V.; Barton, T.J. *J. Chem. Educ.* ***1971***, *48*, 338; Hambly, A.N. *Rev. Pure Appl. Chem.* ***1965***, *15*, 87, 88.

[79] Caskey, D.C.; Damrauer, R.; McGoff, D. *J. Org. Chem.* ***2002***, *67,* 5098.

basicity of amines in THF[80] and in water[81] has been determined, and the basicity of pyridine was examined.[82] Weaker bases have also been examined, and the basicity of carbonyl compound in carbon tetrachloride has been determined.[83]

A class or organic compounds termed *super bases* has been developed. Vinamidine type or Schwesinger proton sponges (see p. 386), **1**,[84] are dubbed super bases and are probably the most powerful organic neutral bases known. The pK_a (p$K_{BH}{}^+$) in MeCN was measure as 31.94. It has been shown that the pK_a values of strong neutral organic (super)bases in acetonitrile are well described by the density functional theory.[85] The fundamental type of proton sponge is 1,8-bis(dimethylamino)-naphthalene, **2** (see p. 386), with a p$K_{BH}{}^+$ of 18.18.[86] Other super base type compounds include amidinazines such as N^1,N^1-dimethyl-N^2-β-(2-pyridylethyl)-formamidine (**3**), p$K_{BH}{}^+$ in DMSO = 25.1,[87] 1,8-bis(tetramethylguanidino) naphthalene, **4**,[88] and quinolino[7,8-*h*]quinolines, such as **5** with a pK_{BH^+} = 12.8.[89]



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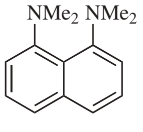

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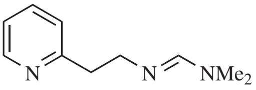

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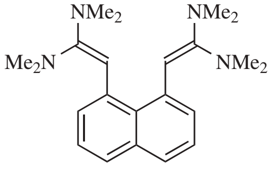

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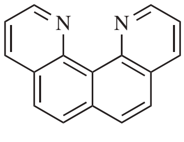

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TABLE 8.2. pK_{HB} Values for Many Types of Bases

Base	Approximate pK_{HB}	Reference
N-Methyl-2-piperidone	2.60	90
$Et_2NCONEt_2$	2.43	90
N-Methyl-2-pyrrolidinone	2.38	90
$PhCONMe_2$	2.23	90
$HCONMe_2$	2.10	90
PhCONHMe	2.03	90
18-crown-6	1.98	91
HCONHMe	1.96	90
15-crown-5	1.82	91
12-crown-4	1.73	91
$PhOCONMe_2$	1.70	90
$Et_2N{-}CN$	1.63	92
$Me_2N{-}CN$	1.56	92
δ-Valerolactone	1.43	93
Oxetane	1.36	91
γ-Butyrolactone	1.32	93
Tetrahydrofuran (THF)	1.28	91
Cyclopentanone	1.27	94
t-BuOMe	1.19	91
Acetone	1.18	94
MeCOOEt	1.07	93
1,4-Dioxane	1.03	91
Et_2O	1.01	91
1,3-Dioxane	0.93	91
1-Methyloxirane	0.97	91
PhCOOMe	0.89	93
MeOCOOMe	0.82	93
PhCHO	0.78	94
Bu_2O	0.75	91
HCOOEt	0.66	93
Me_3CHO	0.65	94
Me_2NO_2	0.41	95
$MeNO_2$	0.27	95
$PhNO_2$	0.30	95
Furan	−0.40	91

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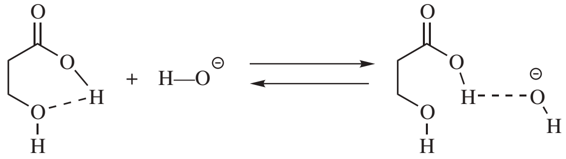
THE MECHANISM OF PROTON-TRANSFER REACTIONS

Proton transfers between oxygen and nitrogen acids and bases are usually extremely fast.[96] In the thermodynamically favored direction they are generally diffusion controlled.[97] In fact, a *normal acid* is defined[98] 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 $<\sim 2$ p*K* units) to that of the acid. The normal acid–base reaction mechanism consists of three steps:

1. $\mathrm{HA} + |\mathrm{B} \rightleftharpoons \mathrm{AH}\bullet\bullet\bullet\bullet|\bullet\mathrm{B}$
2. $\mathrm{AH}\bullet\bullet\bullet\bullet|\bullet\mathrm{B} \rightleftharpoons \mathrm{A}\bullet|\bullet\bullet\bullet\bullet\mathrm{HB}$
3. $\mathrm{A}|\bullet\bullet\bullet\bullet\mathrm{HB} \rightleftharpoons \mathrm{A}| + \mathrm{HB}$

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.[99] In a case such as 3-hydroxypropanoic acid,



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. Other systems are capable of hydrogen bonding, such as 1,2-diols. In the case of cyclohexane-1,2-diols, hydrogen bonding, ion–dipole interactions, polarizability, and stereochemistry all

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[96] For reviews of such proton transfers, see Hibbert, F. *Adv. Phys. Org. Chem.* ***1986***, *22*, 113; Crooks, J.E., in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8; Elsevier, NY, ***1977***, pp. 197–250.

[97] Kinetic studies of these very fast reactions were first carried out by Eigen. See Eigen, M. *Angew. Chem. Int. Ed.* ***1964***, *3*, 1.

[98] See, for example, Hojatti, M.; Kresge, A.J.; Wang, W. *J. Am. Chem. Soc.* ***1987***, *109*, 4023.

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

play a role in determining the acidity.[100] The presence of halogen atoms such as chlorine can lead to hydrogen-bonding effects.[101] 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. 190). See also, the proton sponges mentioned on p. 386. 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.

Proton transfers to or from a carbon atom[102] in most cases are much slower than those strictly between oxygen or nitrogen atoms. At least three factors can be responsible for this,[103] 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[104] behave kinetically as normal acids.[105] It has been reported that carborane acids, such as $H(CHB_{11}H_5Cl_6)$, are the strongest isolable (Lewis-free) Brønsted acids known.[106]
3. There may be considerable reorganization of solvent molecules around the ion as compared to the neutral molecule.[107]

In connection with factors 2 and 3, it has been proposed[103] 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*.

Mechanisms of proton transfer have been studied for many compounds, including the reactions of acids with lactams,[108] amides with various bases,[109] and amines with alkoxide bases.[110]

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[103] See Bernasconi, C.F. *Tetrahedron* ***1985***, *41*, 3219.

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[105] Not all 1-alkynes behave as normal acids; see Aroella, T.; Arrowsmith, C.H.; Hojatti, M.; Kresge, A.J.; Powell, M.F.; Tang, Y.S.; Wang, W. *J. Am. Chem. Soc.* ***1987***, *109*, 7198.

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MEASUREMENTS OF SOLVENT ACIDITY[111]

When a solute is added to an acidic solvent it may become protonated by the solvent. This effect can lead to an enhancement of acidity, as in the effect of using formic acid rather than methanol.[112] An acidity scale has been reported for ionic liquids[113] (see p 415 for a discussion of ionic liquids), and the Lewis acidity of ionic liquids has been established using ir.[114] 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[115] is a measurement that is used for acidic solvents of high dielectric constant.[116] For any solvent, including mixtures of solvents (but the proportions of the mixture must be specified), a value H_0 is defined as

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

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 (p$K_{BH_w^+}$) 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 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

$$h_o = \frac{a_{H^+} f I}{f_{HI^+}}$$

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[111] For fuller treatments, see Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 263–313; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 83–93; Arnett, E.M.; Scorrano, G. *Adv. Phys. Org. Chem.* ***1976***, *13*, 83.

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[116] For a monograph on acidity functions, see Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***. For reviews, see Ref. 111; Cox, R.A.; Yates, K. *Can. J. Chem.* ***1983***, *61*, 2225; Boyd R.H., in Coetzee, J.F.; Ritchie, C.D. *Solute–Solvent Interactions*, Marcel Dekker, NY, ***1969***, pp. 97–218; Vinnik, M.I. *Russ. Chem. Rev.* ***1966***, *35*, 802; Liler, M. *Reaction Mechanisms in Sulfuric Acid*, Academic Press, NY, ***1971***, pp. 26–58.

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,[117] respectively. The parameter H_0 is related to H_0 by

$$H_{\mathrm{o}} = -\log h_{\mathrm{o}}$$

so that H_0 is analogous to pH and H_0 to $[\mathrm{H}^+]$, and indeed in dilute aqueous solution $H_{\mathrm{o}} = \mathrm{pH}$.

The parameter 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, and so on. It is apparent that the H_0 treatment is valid only when $f_{\mathrm{I}}/f_{\mathrm{HI}^+}$ 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.[118] Other acidity scales[119] have been set up, including a scale for C—H acids,[120] among them H_- for bases with a charge of -1, H_{R} for aryl carbinols,[121] H_{C} for bases that protonate on carbon,[122] and H_{A} for unsubstituted amides.[123] 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.[124]

Although most acidity functions have been applied only to acidic solutions, some work has also been done with strongly basic solutions.[125] 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

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[117] For a review of activity coefficient behavior of indicators in acid solutions, see Yates, K.; McClelland, R.A. *Prog. Phys. Org. Chem.* ***1974***, *11*, 323.

[118] For example, see Kresge, A.J.; Barry, G.W.; Charles, K.R.; Chiang, Y. *J. Am. Chem. Soc.* ***1962***, *84*, 4343; Katritzky, A.R.; Waring, A.J.; Yates, K. *Tetrahedron* ***1963***, *19*, 465; Arnett, E.M.; Mach, G.W. *J. Am. Chem. Soc.* ***1964***, *86*, 2671; Jorgenson, M.J.; Hartter, D.R. *J. Am. Chem. Soc.* ***1963***, *85*, 878; Kreevoy, M.M.; Baughman, E.H. *J. Am. Chem. Soc.* ***1973***, *95*, 8178; García, B.; Leal, J.M.; Herrero, L.A.; Palacios, J.C. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1759; Arnett, E.M.; Quirk, R.P.; Burke, J.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1260.

[119] For lengthy tables of many acidity scales, with references, see Cox, R.A.; Yates, K. *Can. J. Chem.* ***1983***, *61*, 2225. For an equation that is said to combine the vast majority of acidity functions, see Zalewski, R.I.; Sarkice, A.Y.; Geltz, Z. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1059.

[120] See Vianello, R.; Maksić, Z.B. *Eur. J. Org. Chem.* ***2004***, 5003.

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[124] Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, p. 278; Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***, p. 21.

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

solvents to abstract a proton from a neutral acid BH.[126] 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,[127] who derived the equation

$$\log \frac{[\mathrm{SH}^+]}{[\mathrm{S}]} + H_o = \phi(H_o + \log[\mathrm{H}^+]) + \mathrm{p}K_{\mathrm{SH}^+}$$

where S is a base that is protonated by an acidic solvent. Thus the slope of a plot of log $([\mathrm{SH}^+]/[\mathrm{S}]) + H_0$ against $H_0 + \log[\mathrm{H}^+]$ 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 $\mathrm{S} + \mathrm{H}^+ \rightleftharpoons \mathrm{SH}^+$ to changing acid concentration. A negative ϕ indicates that the log of the ionization ratio $[\mathrm{SH}^+]/[\mathrm{S}]$ 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. 405) that pertains to acid-base equilibria. A corresponding equation that applies to kinetic data is

$$\log k_\psi + H_0 = \phi(H_o + \log[\mathrm{H}^+]) + \log k_2^0$$

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_2^0 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.[128]

A treatment partially based on the Bunnett–Olsen one is that of Bagno Scorrano, and More O'Ferrall,[129] 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

$$\log \frac{K'}{K'_0} = m^* \log \frac{K}{K_o}$$

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[126] For reviews, see Rochester, C.H. *Q. Rev. Chem. Soc.* ***1966***, *20*, 511; Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***, pp. 234–264; Bowden, K. *Chem. Rev.* ***1966***, *66*, 119 (the last review is reprinted in (Coetzee, J.F.; Ritchie, C.D. *Solute–Solvent Interactions*, Marcel Dekker, NY, ***1969***, pp. 186–215).

[127] Bunnett, J.F.; McDonald, R.L.; Olsen, F.P. *J. Am. Chem. Soc.* ***1974***, *96*, 2855.

[128] More O'Ferrall, R.A. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 976.

[129] Bagno, A.; Scorrano, G.; More O'Ferrall, R.A. *Rev. Chem. Intermed.* ***1987***, *7*, 313. See also, Sampoli, M.; De Santis, A.; Marziano, N.C. *J. Chem. Soc. Chem. Commun.* ***1985***, 110; Cox, R.A. *Acc. Chem. Res.* ***1987***, *20*, 27.

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[130] 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.

A new acidity scale has been developed based on calorimetric measurement of *N*-methylimidazole and *N*-methylpyrrole in bulk solvents.[131] A revised version of this method was shown to give better results in some cases.[132] Another scale of solvent acidities was developed based on the hydrogen-bond donor acidities in aqueous DMSO.[133] It is noted that bond energies, acidities, and electron affinities are related in a thermodynamic cycle, and Kass and Fattahi have shown that by measuring two of these quantities the third can be found.[134]

ACID AND BASE CATALYSIS[135]

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

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[130] Bunnett, J.F. *J. Am. Chem. Soc.* ***1961***, *83*, 4956, 4968, 4973, 4978.

[131] Catalán, J.; Couto, A.; Gomez, J.; Saiz, J.L.; Laynez, J. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 1181.

[132] Abraham, M.H.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 305.

[133] Liu, P.C.; Hoz, S.; Buncel, E. *Gazz. Chim. Ital.* ***1996***, *126*, 31. See also Abraham, M.H.; Zhao, Y.J. *J. Org. Chem.* **2004**, *69*, 4677.

[134] Fattahi, A.; Kass, S.R. *J. Org. Chem.* **2004**, *69*, 9176.

[135] For reviews, see Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, NY, ***1985***, pp. 251–305; Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 315–345; Willi, A.V., in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8, Elsevier, NY, ***1977***, pp. 1–95; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 72–82; Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 159–193; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 163–242; Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley, NY, ***1971***, pp. 19–144.

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*[136]

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

where k is the rate constant for a reaction catalyzed by an acid of ionization constant K_α. According to this equation, when log k is plotted against log K_α for catalysis of a given reaction by a series of acids, a straight line should be obtained with slope 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. 405).

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[137] between a carbon and an oxygen (or a nitrogen), the simplified[138] equation (p. 309)

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

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[136] For reviews, see Klumpp, G.W. *Reactivity in Organic Chemistry*; Wiley, NY, ***1982***, pp. 167–179; Bell, R.P., in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*; Plenum Press, NY, ***1978***, pp. 55–84; Kresge, A.J. *Chem. Soc. Rev.* ***1973***, *2*, 475.

[137] For applications of Marcus theory to proton transfers, see Marcus, R.A. *J. Phys. Chem.* ***1968***, *72*, 891; Kreevoy, M.M.; Konasewich, D.E. *Adv. Chem. Phys.* ***1971***, *21*, 243; Kresge, A.J. *Chem. Soc. Rev.* ***1973***, *2*, 475.

[138] Omitting the work terms.

where

$$\Delta G^{\ddagger}_{\text{int}} = \frac{1}{2}\left(\Delta G_{(0^{\ddagger},0)} + \Delta G_{(C^{\ddagger},C)}\right)$$

can be further simplified: Because proton transfers between oxygen and oxygen (or nitrogen and nitrogen) are much faster than those between carbon and carbon, $\Delta G(_{0},{}^{\ddagger}{}_{0})$ is much smaller than $\Delta G(_{\mathrm{C}},{}^{\ddagger}{}_{\mathrm{C}})$ and we can write[139]

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

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:

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

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 $\mathrm{A} \overset{\mathrm{SH}^{+}}{\rightleftharpoons} \mathrm{AH}^{+}$
Step 2 $\mathrm{AH}^{+} \rightarrow$ 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.[140] Further information can be obtained from the values α and β in the Brønsted catalysis equations, since these are

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[139] Albery, W.J. *Annu. Rev. Phys. Chem.* ***1980***, *31*, 227, p. 244.

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

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; that is, 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; that is, in the transition state the proton has been almost completely transferred. However, cases are known in which these generalizations are not followed,[141] and their theoretical basis has been challenged.[142] In general, the proton in the transition state lies closer to the weaker base.

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.[143] 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

$$\mathrm{A} + \mathrm{:B} \longrightarrow \mathrm{A{-}B}$$

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

$$\mathrm{BF_3} + \mathrm{:NH_3} \longrightarrow \mathrm{F_3}\overset{\ominus}{\mathrm{B}}\rightarrow\overset{\oplus}{\mathrm{N}}\mathrm{H_3}$$

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. Lewis acids $SnCl_4$ and SO_3 have eight, but their central elements, not being in the first row of the Periodic table, have room for 10 or 12. Other Lewis acids are simple cations, like Ag^+. The simple reaction

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[141] See, for example, Bordwell, F.G.; Boyle, Jr., W.J. *J. Am. Chem. Soc.* ***1972***, *94*, 3907; Davies, M.H. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1018; Agmon, N. *J. Am. Chem. Soc.* ***1980***, *102*, 2164; Murray, C.J.; Jencks, W.P. *J. Am. Chem. Soc.* ***1988***, *110*, 7561.

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

[143] For a monograph on Lewis acid–base theory, see Jensen, W.B. *The Lewis Acid–Base Concept*, Wiley, NY, ***1980***. For a discussion of the definitions of Lewis acid and base, see Jensen, W.B. *Chem. Rev.* ***1978***, *78*, 1.

$A + \bar{B} \rightarrow A{-}B$ is not very common in organic chemistry, but the scope of the Lewis picture is much larger because reactions of the types

$$\begin{array}{ccccccc} A^1 & + & A^2{-}B & \longrightarrow & A^1{-}B & + & A^2 \\ B^1 & + & A{-}B^2 & \longrightarrow & A{-}B^1 & + & B^2 \\ A^1{-}B^1 & + & A^2{-}B^2 & \longrightarrow & A^1{-}B^2 & + & A^2{-}B^1 \end{array}$$

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. An *ab initio* analysis of the factors that determine Lewis versus Lowry–Brønsted acidity–basicity is available.[144]

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*.[145] Examples are

$$\mathrm{Me_3B} + \mathrm{LiMe} \longrightarrow \underset{\text{An ate complex}}{\mathrm{Me_4B^-\ Li^+}}$$

$$\mathrm{Ph_5Sb} + \mathrm{LiPh} \longrightarrow \underset{\text{An ate complex}}{\mathrm{Ph_6Sb^-\ Li^+}}$$

The ate complexes are analogous to the onium salts formed when a Lewis base expands its valence, for example,

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

Far fewer quantitative measurements have been made of Lewis acid strength compared to that of Brønsted acids.[146] A simple table of Lewis acidities based on some quantitative measurement (e.g., that given for Brønsted acids in Table 8.1) is not feasible because Lewis acidity depends on the nature of the base and any solvent that can function as a base. For example, lithium perchlorate functions as a weak Lewis acid in ether.[147] Qualitatively, the following approximate sequence

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[144] Rauk, A.; Hunt, I.R.; Keay, B.A. *J. Org. Chem.* ***1994***, *59*, 6808.

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

[146] For reviews of the quantitative aspects of Lewis acidity, see Satchell, D.P.N.; Satchell, R.S. *Q. Rev. Chem. Soc.* ***1971***, *25*, 171; *Chem. Rev.* ***1969***, *69*, 251. See also Maria, P.; Gal, J. *J. Phys. Chem.* ***1985***, *89*, 1296; Larson, J.W.; Szulejko, J.E.; McMahon, T.B. *J. Am. Chem. Soc.* ***1988***, *110*, 7604; Sandström, M.; Persson, I.; Persson, P. *Acta Chem. Scand.* ***1990***, *44*, 653; Laszlo, P.; Teston-Henry, M. *Tetrahedron Lett.* ***1991***, *32*, 3837.

[147] Springer, G.; Elam, C.; Edwards, A.; Bowe, C.; Boyles, D.; Bartmess, J.; Chandler, M.; West, K.; Williams, J.; Green, J.; Pagni, R.M.; Kabalka, G.W. *J. Org. Chem.* ***1999***, *64*, 2202.

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*[148] or *softness* of the acid or base.[149] 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 8.3.[150] The treatment has also been made quantitative,[151] 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.[152] The softness, σ, is the reciprocal of

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[148] See Ayers, P.W.; Parr, R.G. *J. Am. Chem. Soc.* ***2000***, *122*, 2010.

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

[150] Taken from larger listings, in Pearson, R.G. Ref. 149.

[151] Pearson, R.G. *Inorg. Chem.* ***1988***, *27*, 734; *J. Org. Chem.* ***1989***, *54*, 1423. See also, Orsky, A.R.; Whitehead M.A. *Can. J. Chem.* ***1987***, *65*, 1970.

[152] For a computational study of proton and electron affinities see Sauers, R.R. *Tetrahedron* ***1999***, *55*, 10013.

TABLE 8.3. Hard and Soft Acids and Bases[150]

Hard Bases	Soft Bases	Borderline Cases
H_2O	OH^- F^-	R_sS RSH RS^- $ArNH_2C_5H_5N$
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 Cases**
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)		

η. Values of η for some molecules and ions are given in Table 8.4.[153] 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 $X^\bullet$.[154] Other methods are also needed to apply the treatment to polyatomic cations.[154]

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).*[155] 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 form ionic bonds.

One application of the first rule given above is found in complexes between alkenes or aromatic compounds and metal ions (p. 376). Alkenes and aromatic rings

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

[154] Pearson, R.G. *J. Am. Chem. Soc.* ***1988***, *110*, 7684.

[155] For proofs of this principle, see Chattaraj, P.K.; Lee, H.; Parr, R.G. *J. Am. Chem. Soc.* ***1991***, *113*, 1855.

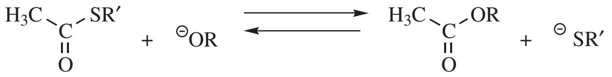
TABLE 8.4. Some Absolute Hardness Values in Electron Volts[151]

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.

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:

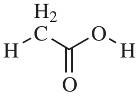


The HSAB principle predicts that the equilibrium should lie to the right, because the hard acid CH_3CO^+ should have a greater affinity for the hard base RO^- than for the soft base RS^-. Indeed, thiol esters are easily cleaved by RO^- or hydrolyzed by dilute base ($^-$OH is also a hard base).[156] Another application of the rule is discussed on p. 493.[157] The HSAB principles have been applied to analyze the reactivity of ketone and ester enolates,[158] and in analyzing catalyst selectivity in synthesis.[159]

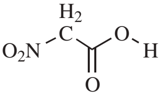
THE EFFECTS OF STRUCTURE ON THE STRENGTHS OF ACIDS AND BASES[160]

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.[161] 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. 19. In general, changes in substituents can have an effect on acidity. As an example of the influence of field effects on acidity, we may compare the acidity of acetic acid and nitroacetic acid:



pK_a = 4.76



pK_a = 1.68

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

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[156] Wolman, Y., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, p. 677; Maskill, H. *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford ***1985***, p. 159.

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

[158] Méndez, F.; Gázguez, J.L. *J. Am. Chem. Soc.* ***1994***, *116*, 9298.

[159] Woodward, S. *Tetrahedron* ***2002***, *58*, 1017.

[160] For a monograph, see Hine, J. *Structural Effects on Equilibria in Organic Chemistry*, Wiley, NY, ***1975***. For reviews, see Taft, R.W. *Prog. Phys. Org. Chem.* ***1983***, *14*, 247; Petrov, E.S. *Russ. Chem. Rev.* ***1983***, *52*, 1144 (NH acids); Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 86–110; Barlin, G.B.; Perrin, D.D., in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 1; Wiley, NY, ***1972***, pp. 611–676. For discussions, see Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 521; Barlin, G.B.; Perrin, D.D. *Q. Rev. Chem. Soc.* ***1966***, *20*, 75; Thirot, G. *Bull. Soc. Chim. Fr.* ***1967***, 3559; Liler, M. *Reaction Mechanisms in Sulfuric acid*, Academic Press, NY, ***1971***, pp. 59–144. For a monograph on methods of estimating pK values by analogy, extrapolation, and so on, see Perrin, D.D.; Dempsey, B.; Serjeant, E.P. pK_a *Prediction for Organic Acids and Bases*, Chapman and Hall, NY, ***1981***.

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

nitroacetic acid (compared with the anion of acetic acid) and, as the pK_a values indicate, nitroacetic acid is ~1000 times stronger than acetic acid.[162] 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,[163] compared with Ph_3CH, with a pK_a of 31.5 (Table 8.1), an acidity enhancement of ~10^{15}. Table 8.5 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. 390–394).[164] The influence of various substituents on the acidity of acetic acid has been calculated,[165] Substituent effects for weak acids, such as phenols and benzyl alcohols, have been discussed.[166]

6

Field effects are important in benzoic acid derivatives, and the pK_a of the acid will vary with the nature and placement of the "X" group in **6**.[167] The pK_a of 3-OMe **6** is 5.55, but 4-OMe **6** is 6.02 in 50% aq. methanol,[168] compared with a pK_a of 5.67 when X = H. When X = 4-NO_2, the pK_a is 4.76 and 4-Br is 5.36.[157] The pK_a of 2,6-diphenylbenzoic acid is 6.39.[169]

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[162] For a review of the enhancement of acidity by NO_2, see Lewis, E.S., in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 715–729.

[163] Filler, R.; Wang, C. *Chem. Commun.* ***1968***, 287.

[164] For discussions, see Edward, J.T. *J. Chem. Educ.* ***1982***, *59*, 354; Schwartz, L.M. *J. Chem. Educ.* ***1981***, *58*, 778.

[165] Headley, A.D.; McMurry, M.E.; Starnes, S.D. *J. Org. Chem.* ***1994***, *59*, 1863.

[166] Wiberg, K.B. *J. Org. Chem.* ***2003***, *68*, 875.

[167] For calculated gas-phase acidities of substituted benzoic acids, see Wiberg, K. B. *J. Org. Chem.* ***2002***, *67*, 4787.

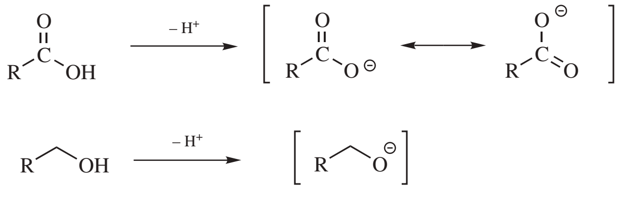
[168] DeMaria, P.; Fontana, A.; Spinelli, D.; Dell'Erba, C.; Novi, M.; Petrillo, G.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 649.

[169] Chen, C.-T.; Siegel, J.S. *J. Am. Chem. Soc.* ***1994***, *116*, 5959. Several 2,6-diaryl derivatives are also reported. See also Sotomatsu, T.; Shigemura, M.; Murata, Y.; Fujita, T. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 3157.

TABLE 8.5. The p*K* Values for Some Acids[40]

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_3COOH	0.65
$CH_3(CH_2)_nCOOH$	4.82–4.95		
($n = 2$–7)		O_2NCH_2COOH	1.68
$(CH_3)_2CHCOOH$	4.86	$(CH_3)_3N^HCH_2COOH$	1.83
$(CH_3)_3CCOOH$	5.05	$HOOCCH_2COOH$	2.83
		$PhCH_2COOH$	4.31
FCH_2COOH	2.66		
$ClCH_2COOH$	2.86	$^-OOCCH_2COOH$	5.69
$BrCH_2COOH$	2.86		
ICH_2COOH	3.12	$^-O_3SCH_2COOH$	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		

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[170] compared with primary alcohols.



The $RCOO^-$ ion is stabilized by resonance not available to the RCH_2O^- ion (or to RCOOH).[171] 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

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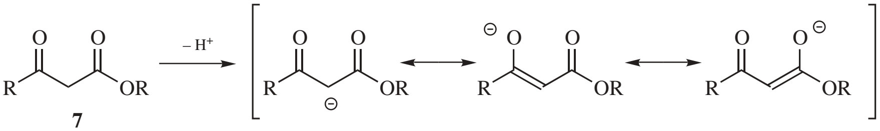
[170] See Exner, O.; Čársky, P. *J. Am. Chem. Soc.* ***2001***, *123*, 9564. See also, Liptak, M.D.; Shields, G.C. *J. Am. Chem. Soc.* ***2001***, *123*, 7314.

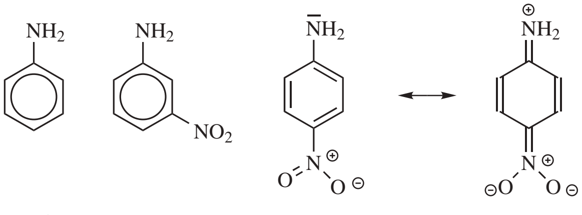
[171] It has been contended that resonance delocalization plays only a minor role in the increased strength of carboxylic acids compared to alcohols, and the "…higher acidity of acids arises principally because the electrostatic potential of the acidic hydrogens is more positive in the neutral acid molecule…": Siggel, M.R.; Streitwieser, Jr., A.; Thomas, T.D. *J. Am. Chem. Soc.* ***1988***, *110*, 8022; Thomas, T.D.; Carroll, T.X.; Siggel, M.R. *J. Org. Chem.* ***1988***, *53*, 1812. For contrary views, see Exner, O. *J. Org. Chem.* ***1988***, *53*, 1810; Dewar, M.J.S.; Krull, K.L. *J. Chem. Soc. Chem. Commun.* ***1990***, 333; Perrin, D.D. *J. Am. Chem. Soc.* ***1991***, *113*, 2865. See also, Godfrey, M. *Tetrahedron Lett.* ***1990***, *31*, 5181.

concentrated than in RCH_2O^-.The same effect is found in other compounds containing a C=O or CN group. Thus amides $RCONH_2$ are more acidic than amines RCH_2NH_2; esters RCH_2-COOR′ 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 of charge); for example, β-keto esters (see **7**) are more acidic than simple ketones or carboxylic esters (Table 8.1). The influence of substituents in the α-position of substituted ethyl acetate derivatives has been studied.[172] Extreme examples of this effect are found in the molecules tricyanomethane $(NC)_3CH$, with a pK_a of −5 (Table 8.1, p. 359), and 2-(dicyanomethylene)-1,1,3,3-tetracyanopropene$(NC)_2$ C=C$[CH(CN)_2]_2$, whose first pK_a is below −8.5 and whose second pK_a is −2.5.



7

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 *p*-nitroaniline is weaker still, though the −*I* effect should be less because of the greater distance. It is noted that the pK_a values reported are those of the conjugate acid, the ammonium ion.[173] We can explain this result by taking into account the canonical form **A**. Because **A** contributes to the resonance hybrid,[174] 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.[175]



4.60 2.47 1.11 **A**

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[172] Goumont, R.; Magnier, E.; Kizilian, E.; Terrier, F. *J. Org. Chem.* ***2003***, *68*,6566.

[173] Smith, J.W. in Patai, S. *The Chemistry of the Amino Group;* Wiley, NY, ***1968***, pp. 161–204.

[174] See, however, Lipkowitz, K.B. *J. Am. Chem. Soc.* ***1982***, *104*, 2647; Krygowski, T.M.; Maurin, J. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 695.

[175] Liptak, M.D.; Gross, K.C.; Seybold, P.G.; Feldus, S.; Shields, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 6421.

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. $$$). 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 $H_3O^+ > H_3S^+ > H_3Se^+$.[176]

Lewis acidity is also affected by Periodic table considerations. In comparing acid strengths of Lewis acids of the form MX_n:[146]

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 $AlCl_3$.[177]

4. *Statistical Effects.* In a symmetrical diprotic acid, the first dissociation constant is twice as large as expected since there are two equivalent ionizable

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[176] Taft, R.W. *Prog. Phys. Org. Chem.* ***1983***, *14*, 247, see pp. 250–254.

[177] 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.

TABLE 8.6. 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

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 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.[178]

5. *Hydrogen Bonding*. Internal hydrogen bonding can greatly influence acid or base strength. For example, the pK 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 8.6 shows the order of base strength of simple amines when compared against acids of various size.[179] 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. 48). For example, *o*-*tert*-butylbenzoic acid is ~10 times as strong as the para isomer, because the carboxyl group is forced out of the plane by the *tert*-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.

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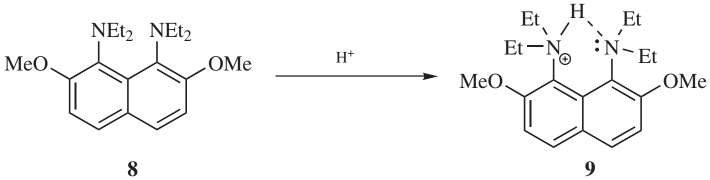
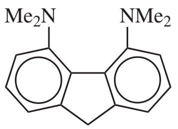
[178] The effect discussed here is an example of a symmetry factor. For an extended discussion, see Eberson, L., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 211–293.

[179] Brown, H.C. *J. Am. Chem. Soc.* ***1945***, *67*, 378, 1452, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 53–64. See also, Brown, H.C.; Krishnamurthy, S.; Hubbard, J.L. *J. Am. Chem. Soc.* ***1978***, *100*, 3343.



8 **9**

Steric effects can also be caused by other types of strain. 1,8-Bis(diethylamino)-2,7-dimethoxynaphthalene (**8**) is an extremely strong base for a tertiary amine (pK_a of the conjugate acid = 16.3; compare *N,N*-dimethylaniline, pK_a = 5.1), but proton transfers to and from the nitrogen are exceptionally slow; slow enough to be followed by a UV spectrophotometer.[180] Compound **8** is severely strained because the two nitrogen lone pairs are forced to be near each other.[181] 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 **9**).



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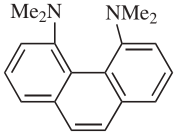

11

The same effects are found in 4,5-bis(dimethylamino)fluorene (**10**)[182] and 4,5-bis(dimethylamino)phenanthrene (**11**).[183] Compounds, such as **8**, **10**, and **11**, are known as *proton sponges*.[184] The basicity of proton sponge has been calculated as the sum of the proton affinity[152] of an appropriate reference monoamine, the strain released on protonation, and the energy of the intramolecular hydrogen bond formed on protonation.[185] Another type of proton sponge is quino[7,8-*h*]quinoline (**12**).[186] Protonation of this compound also gives a stable mono-protonated ion similar to **9**, but the steric hindrance found in **8**, **10**, and **11** is absent. Therefore, **12** is a much stronger base than quinoline (**13**) (pK_a values of the conjugate acids are 12.8 for **12** and 4.9 for **13**), but proton transfers are not abnormally slow. A cyclam-like macrocyclic

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[180] Barnett, G.H.; Hibbert, F. *J. Am. Chem. Soc.* ***1984***, *106*, 2080; Hibbert, F.; Simpson, G.R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 243, 613.

[181] For a review of the effect of strain on amine basicities, see Alder, R.W. *Chem. Rev.* ***1989***, *89*, 1215.

[182] Staab, H.A.; Saupe, T.; Krieger, C. *Angew. Chem. Int. Ed.* ***1983***, *22*, 731.

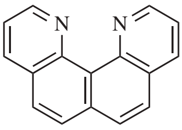
[183] Saupe, T.; Krieger, C.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1986***, *25*, 451.

[184] For a review, see Staab, H.A.; Saupe, T. *Angew. Chem. Int. Ed.* ***1988***, *27*, 865.

[185] Howard, S.T. *J. Am. Chem. Soc.* ***2000***, *122*, 8238.

[186] Krieger, C.; Newsom, I.; Zirnstein, M.A.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1989***, *28*, 84. See also, Schwesinger, R.; Missfeldt, M.; Peters, K.; Schnering, H.G. von *Angew. Chem. Int. Ed.* ***1987***, *26*, 1165; Alder, R.W.; Eastment, P.; Hext, N.M.; Moss, R.E.; Orpen, A.G.; White, J.M. *J. Chem. Soc. Chem. Commun.* ***1988***, 1528; Staab, H.A.; Zirnstein, M.A.; Krieger, C. *Angew. Chem. Int. Ed.* ***1989***, *28*, 86.

tetramine (**15**) was prepared by a coupling reaction of bispidine, and was shown to be a new class of proton sponge.[187]



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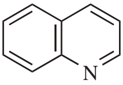

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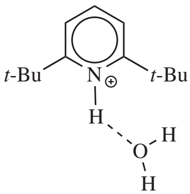

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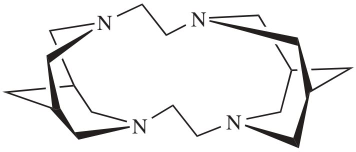
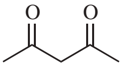


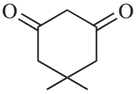
15

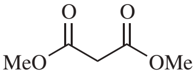
Chiral Lewis acids are known. Indeed, an air stable and storable chiral Lewis acid catalyst has been prepared, a chiral zirconium catalyst combined with molecular sieves powder.[188] Association of a bulky silicon group with the bis(trifluoromethanesulfonyl)imide anion leads to enhancement of the electrophilic character of R_3SiNTf_2. The presence of a chiral substituent derived from (−)-myrtenal on the silicon atom led to a chiral silicon Lewis acid.[189]

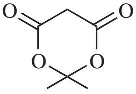
Another type of steric effect is the result of an entropy effect. The compound 2,6-di-*tert*-butylpyridine is a weaker base than either pyridine or 2,6-dimethylpyridine.[190] The reason is that the conjugate acid (**14**) is less stable than the conjugate acids of non-sterically hindered pyridines. In all cases, the conjugate acids are hydrogen bonded to a water molecule, but in the case of **14** the bulky *tert*-butyl groups restrict rotations in the water molecule, lowering the entropy.[191]

The conformation of a molecule can also affect its acidity. The following pK_a values were determined for these compounds:[192]









	16	**17**	**18**	**19**
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 **16** is a stronger acid than **18**. But cyclization of **16** to **17** increases the acidity by only 2.1 pK units while cyclization of **18** to **19**

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[187] Miyahara, Y.; Goto, K.; Inazu, T. *Tetrahedron Lett.* ***2001***, *42*, 3097.

[188] Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* ***2002***, *4*, 3395.

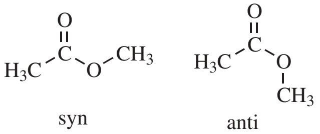
[189] Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett* ***2000***, *41*, 9651

[190] Brown, H.C.; Kanner, B. *J. Am. Chem. Soc.* ***1953***, *75*, 3865; ***1966***, *88*, 986.

[191] Hopkins, Jr., H.P.; Janagirdar, D.V.; Moulik, P.S.; Aue, D.H.; Webb, H.M.; Davidson, W.R.; Pedley; M.D. *J. Am. Chem. Soc.* ***1984***, *106*, 4341; Meot-Ner, M.; Smith, S.C. *J. Am. Chem. Soc.* ***1991***, *113*, 862, and references cited therein. See also, Benoit, R.L.; Fréchette, M.; Lefebvre, D. *Can. J. Chem.* ***1988***, *66*, 1159.

[192] Arnett, E.M.; Harrelson Jr., J.A. *J. Am. Chem. Soc.* ***1987***, *109*, 809.

increases it by 8.6 units. Indeed, it has long been known that **19** (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.[193] Both found that loss of a proton is easier by ~5 kcal mol^{-1} (21 kJ mol^{-1}) for the syn than for the anti conformer of the ester. In an acyclic molecule like **18**, the preferred conformations are anti, but in Meldrum's acid (**19**) the conformation on both sides is constrained to be syn.

Facial differences in proton reactivity can lead to enantioselective deprotonation. A more common way to achieve enantioselective deprotonation is to use a chiral base and/or a chiral complexing agent. Enantioselective deprotonation in cyclic ketones has been studied.[194] Enantioselective deprotonation with heterodimer bases has been studied.[195]

When a Lewis acid coordinates to a base, the resulting complex can have conformational properties that influence reactivity. Coordination of $SnCl_4$ with aldehydes and esters, for example, leads to a complex where the conformation is determined by interactions of the $C{=}O{\bullet\bullet\bullet}SnCl_4$ unit with substituents attached to the carbonyl.[196]

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).

A recent development in understanding the reactivity of bases has focused on their structures in solution and in the crystalline state. Due to the importance of dialkyl amide bases, there is a significant body of work, led by Williard and by Collum, that has attempted to understand the structures of

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[193] Wang, X.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 1870; Wiberg, K.B.; Laidig, K.E. *J. Am. Chem. Soc.* ***1988***, *110*, 1872.

[194] Majewski, M.; Wang, F. *Tetrahedron* ***2002***, *58*, 4567.

[195] Amedjkouh, M. *Tetrahedron Asymm.* ***2004***, *15*, 577.

[196] Gung, B.W.; Yanik, M.M. *J. Org. Chem.* ***1996***, *61*, 947.

these reactive molecules. It is clear that they are aggregates. Note that the simplest member of the amide base family, lithium amide ($LiNH_2$) was shown to be monomeric and unsolvated, as determined using a combination of gas-phase synthesis and millimeter–submillimeter wave spectroscopy.[197] Note that monomeric $LiNH_2$ and $LiNMe_2$ are planar.[198] Lithium diisopropylamide ($LiNiPr_2$, LDA) was isolated from a THF solution and X-ray crystallography revealed a dimeric structure (**20**; R = *i*Pr, S = THF) in the solid state.[199] Lithium diisopropylamide was also shown to be a dimer in solutions of THF[200] and/or HMPA (see **20**, R = *i*Pr and S = THF, HMPA).[201] In the presence of HMPA, many derivatives **20** tend to be mixed aggregates.[202] Extremely hindered $LiNR_2$ (R = 2-adamantyl) are monomeric under all conditions.[203] In hydrocarbon solvents, lithium tetramethylpiperidide [LTMP, RR'NLi where $RR' = -CMe_2(CH_2)_3C(Me_2)-$] forms cyclic trimers and tetramers, with the tetrameric species predominating.[204] In THF, lithium hexamethyldisilazide [LHMDS, $(Me_3Si)_2NLi$] forms a five-coordinate tetrasolvate [$(Me_3Si)_2NLi(thf)_4$],[205] but in ether there is an equilibrium mixture of monomer and dimer.[206] A review is available that discusses the solution structures of amide bases $LiNR_2$.[207] Chiral lithium amide bases are known and they show similar behavior in solution.[208] Chelation effects are common in enantio-enriched amide bases, which also form aggregates.[209] The aggregation state of lithium phenylacetonitrile has been studied.[210] Dianion aggregates can be generated, and in the case of the lithiation reaction of *N*-silyl allylamine, X-ray structure determination showed the presence of three

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[197] Grotjahn, D.B.; Sheridan, P.M.; Al Jihad, I.; Ziurys, L.M. *J. Am. Chem. Soc.* ***2001***, *123*, 5489.

[198] Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C.; Silvi, B. *J. Org. Chem.* ***2001***, *66*, 6476.

[199] Williard P.G.; Salvino, J.M. *J. Org. Chem.* ***1993***, *58*, 1. For a study of the oligomer structure of LDA at low ligand concentrations, see Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2001***, *123*, 199.

[200] Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* ***1992***, *33*, 3769.

[201] Aubrecht, K.B.; Collum, D.B. *J. Org. Chem.* ***1996***, *61*, 8674.

[202] Romesberg, F.E.; Collum, D.B. *J. Am.Chem. Soc.* ***1994***, *116*, 9198, 9187. For a study of other mixed aggregates see Thomas, R.D.; Huang, J. *J. Am. Chem. Soc.* ***1999***, *121*, 11239.

[203] Sakuma, K.; Gilchrist, J.H.; Romesberg, F.E.; Cajthami, C.E.; Collum, D.B. *Tetrahedron Lett.* ***1993***, *34*, 5213.

[204] Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 7949.

[205] Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1995***, *117*, 9863. See also, Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1996***, *118*, 2217, 3529. See Romesberg, F.E.; Bernstein, M.P.; Gilchrist, J.H.; Harrison, A.T.; Fuller, D.J.; Collum, D.B. *J. Am. Chem. Soc.* ***1993***, *115*, 3475 for the structure in HMPA.

[206] Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 6009.

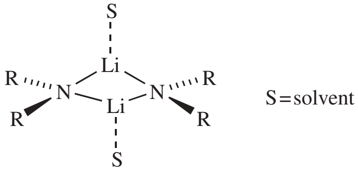
[207] Collum, D.B. *Acc. Chem. Res.* ***1993***, *26*, 227. For NMR studies of $LiNEt_2$ and ring laddering see Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1999***, *121*, 10198.

[208] Hilmersson, G.; Davidsson, Ö. *J. Org. Chem.* ***1995***, *60*, 7660. See also, O'Brien, P. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 1439. See also, Sott, R.; Grandander, J.; Dinér, P.; Hilmersson, G. *Tetrahedron Asymm.* ***2004***, *15*, 267.

[209] Arvidsson, P.I.; Hilmersson, G.; Ahlberg, P. *J. Am. Chem. Soc.* ***1999***, *121*, 183.

[210] Carlier, P.R.; Madura, J.D. *J. Org. Chem.* ***2002***, *67*, 3832.

uniquely different aggregates.[211] A mixed aggregate is formed when the lithium enolate of a ketone is mixed with a lithium amide.[212]



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Similar information is available for other bases. Lithium phenoxide (LiOPh) is a tetramer in THF.[213] Lithium 3,5-dimethylphenoxide is a tetramer in ether, but addition of HMPA leads to dissociation to a monomer.[214]

Enolate anions are nucleophiles in reactions with alkyl halides (reaction **10-68**), with aldehydes and ketones (reactions **16-34**, **16-36**) and with acid derivatives (reaction **16-85**). Enolate anions are also bases, reacting with water, alcohols and other protic solvents, and even the carbonyl precursor to the enolate anion. Enolate anions exist as aggregates, and the effect of solvent on aggregation and reactivity of lithium enolate anions has been studied.[215] The influence of alkyl substitution on the energetics of enolate anions has been studied.[216]

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 temperature (p. 364) 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.[217] If a base is more solvated than its conjugate acid, its stability is increased relative to the conjugate acid. For example,

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[211] Williard, P. G.; Jacobson, M. A. *Org. Lett.* ***2000***, *2*, 2753. For the structure and bonding of dilithiodiamines see Pratt, L.M.; Mu, R. *J. Org. Chem.* ***2004***, *69*, 7519.

[212] Sun, C.; Williard, P.G. *J. Am. Chem. Soc.* ***2000***, *122* , 7829. See also, Pratt, L.M.; Streitwieser, A. *J. Org. Chem.* ***2003***, *68*, 2830.

[213] Jackman, L.M.; Çizmeciyan, D.; Williard, P.G.; Nichols, M.A. *J. Am. Chem. Soc.* ***1993***, *115*, 6262.

[214] Jackman, L.M.; Chen, X. *J. Am. Chem. Soc.* ***1992***, *114*, 403.

[215] Streitwieser, A.; Juaristi, E.; Kim, Y.-J.; Pugh, J.K. *Org. Lett.* ***2000***, *2*, 3839.

[216] Alconcel, L.S.; Deyerl, H.-J.; Continetti, R.E. *J. Am. Chem. Soc.* ***2001***, *123*, 12675.

[217] For reviews of the effects of solvent, see Epshtein, L.M.; Iogansen, A.V. *Russ. Chem. Rev.* ***1990***, *59*, 134; Dyumaev, K.M.; Korolev, B.A. *Russ. Chem. Rev.* ***1980***, *49*, 1021. For a review of the effects of the solvent DMSO, see Taft, R.W.; Bordwell, F.G. *Acc. Chem. Res.* ***1988***, *21*, 463. For determination of pK_a values of various compounds in acetonitrile see Heemstra, J.M.; Moore, J.S. *Tetrahedron* ***2004***, *60*, 7287.

Table 8.6 shows that toward the proton, where steric effects are absent, methylamine is a stronger base than ammonia and dimethylamine is stronger still.[218] 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.[219] Thus, NH_4^+ is much better hydrated (by hydrogen bonding to the water solvent) than NH_3 because of its positive charge.[220] It has been estimated that this effect contributes ~11 p*K* units to the base strength of ammonia.[221] When methyl groups replace hydrogen, this difference in hydration decreases[222] until, for trimethylamine, it contributes only ~6 p*K* units to the base strength.[179] 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,[223] 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.[224] Aniline

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[218] For a review of the basicity of amines, see Smith, J.W., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 161–204.

[219] Trotman-Dickenson, A.F. *J. Chem. Soc.* ***1949***, 1293; Pearson, R.G.; Williams, F.V. *J. Am. Chem. Soc.* ***1954***, *76*, 258; Hall, Jr., H.K. *J. Am. Chem. Soc.* ***1957***, *79*, 5441; Arnett, E.M.; Jones III, F.M; Taagepera, M.; Henderson, W.G.; Beauchamp, J.L.; Holtz, D.; Taft, R.W. *J. Am. Chem. Soc.* ***1972***, *94*, 4724; Aue, D.H.; Webb, H.M.; Bowers, M.T. *J. Am. Chem. Soc.* ***1972***, *94*, 4726; ***1976***, *98*, 311, 318; Mucci, A.; Domain, R.; Benoit, R.L. *Can. J. Chem.* ***1980***, *58*, 953. See also Drago, R.S.; Cundari, T.R.; Ferris, D.C. *J. Org. Chem.* ***1989***, *54*, 1042.

[220] For discussions of the solvation of ammonia and amines, see Jones III, F.M.; Arnett, E.M. *Prog. Phys. Org. Chem.* ***1974***, *11*, 263; Grunwald, E.; Ralph, E.K. *Acc. Chem. Res.* ***1971***, *4*, 107.

[221] Condon, F.E. *J. Am. Chem. Soc.* ***1965***, *87*, 4481, 4485.

[222] 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, Y.K.; Kebarle, P. *Can. J. Chem.* ***1981***, *59*, 151.

[223] For reviews of acidities and basicities in the gas phase, see Liebman, J.F. *Mol. Struct. Energ.* ***1987***, *4*, 49; Dixon, D.A.; Lias, S.G. *Mol. Struct. Energ.* 1987, *2*, 269; Bohme, D.K., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 731–762; Bartmess, J.E.; McIver, Jr., R.T., in Bowers, M.T. *Gas Phase Ion Chemistry*, Vol. 2, Academic Press, NY, ***1979***, pp. 88–121; Kabachnik, M.I. *Russ. Chem. Rev.* ***1979***, *48*, 814; Kebarle, P. *Annu. Rev. Phys. Chem.* ***1977***, *28*, 445; Arnett, E.M. *Acc. Chem. Res.* ***1973***, *6*, 404. For a comprehensive table of gas-phase basicities, see Lias, S.G.; Liebman, J.F.; Levin, R.D. *J. Phys. Chem. Ref. Data*, ***1984***, *13*, 695. See also the tables of gas-phase acidities and basicities in the following articles, and their cited references: Meot-Ner, M.; Kafafi, S.A. *J. Am. Chem. Soc.* ***1988***, *110*, 6297; Headley, A.D. *J. Am. Chem. Soc.* ***1987***, *109*, 2347; McMahon, T.B.; Kebarle, P. *J. Am. Chem. Soc.* ***1985***, *107*, 2612; ***1977***, *99*, 2222, 3399; Wolf, J.F.; Staley, R.H.; Koppel, I.; Bartmess, J.E.; Scott, J.A.; McIver, Jr., R.T. *J. Am. Chem. Soc.* ***1979***, *101*, 6046; Fujio, M.; McIver, Jr., R.T.; Taft, R.W. *J. Am. Chem. Soc.* ***1981***, *103*, 4017; Lau, Y.K.; Nishizawa, K.; Tse, A.; Brown, R.S.; Kebarle, P. *J. Am. Chem. Soc.* ***1981***, *103*, 6291.

[224] Munson, M.S.B. *J. Am. Chem. Soc.* ***1965***, *87*, 2332; Brauman, J.I.; Riveros, J.M.; Blair, L.K. *J. Am. Chem. Soc.* ***1971***, *93*, 3914; Briggs, J.P.; Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1972***, *94*, 5128; Aue, D.H.; Webb H.M.; Bowers, M.T. *J. Am. Chem. Soc.* ***1972***, *94*, 4726; ***1976***, *98*, 311, 318.

too, in the gas phase, is a stronger base than NH_3,[225] 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[226] and pyrrole[227] are both much less basic than NH_3 in aqueous solution (pyrrole[228] is neutral in aqueous solution), but *more* basic in the gas phase. These examples in particular show how careful one must be in attributing relative acidities or basicities to any particular effect. Solvent has a significant influence on the Hammett reaction constant (p. 679), which influences the acidity of substituted benzoic acids.[229]

In the case of Lewis acids, protic solvents such as water or alcohol can strongly influence their reactivity, cause it to react via an alternative path to the one desired, or even cause decomposition. Recently, rare earth metal triflates were used to develop water tolerant Lewis acids that can be used in many organic reactions.[230]

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.[231] 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,[232] though weaker in aqueous solution (Table 8.5).

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[225] Briggs, J.P.; Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1972***, *94*, 5128; Dzidic, I. *J. Am. Chem. Soc.* ***1972***, *94*, 8333; Ikuta, S.; Kebarle, P. *Can. J. Chem.* ***1983***, *61*, 97.

[226] Taft, R.W.; Taagepera, M.; Summerhays, K.D.; Mitsky, J. *J. Am. Chem. Soc.* ***1973***, *95*, 3811; Briggs, J.P.; Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1972***, *94*, 5128.

[227] Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1973***, *95*, 3504.

[228] For a review of the basicity and acidity of pyrroles, see Catalan, J.; Abboud, J.L.M.; Elguero, J. *Adv. Heterocycl. Chem.* ***1987***, *41*, 187.

[229] Bartnicka, H.; Bojanowska, I.; Kalinowski, M.K. *Aust. J. Chem.* ***1993***, *46*, 31.

[230] Kobayashi, S. *Synlett*, ***1994***, 689.

[231] Baird, N.C. *Can. J. Chem.* ***1969***, *47*, 2306; Arnett, E.M.; Small, L.E.; McIver, Jr., R.T.; Miller, J.S. *J. Am. Chem. Soc.* ***1974***, *96*, 5638; Blair, L.K.; Isolani, P.C.; Riveros, J.M. *J. Am. Chem. Soc.* ***1973***, *95*, 1057; McIver, Jr., R.T.; Scott, J.A.; Riveros, J.M. *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, J.E.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1977***, *99*, 4163.

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

The evidence in these and other cases[233] 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.[234] 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.[235] Polarizability effects on anionic centers are a major factor in gas-phase acid–base reactions.[236]

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.[237]

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.[238] Two examples are shown in Table 8.7.[239] Resonance and field effects of functional groups therefore affect the acidity of RCOOH in two distinct ways. They affect the enthalpy (electron withdrawing 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).

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[233] Brauman, J.I.; Blair, L.K. *J. Am. Chem. Soc.* ***1971***, *93*, 4315; Kwart, H.; Takeshita, T. *J. Am. Chem. Soc.* ***1964***, *86*, 1161; Fort, Jr., R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1964***, *86*, 4194; Holtz, H.D.; Stock, L.M. *J. Am. Chem. Soc.* ***1965***, *87*, 2404; Laurie, V.W.; Muenter, J.S. *J. Am. Chem. Soc.* ***1966***, *88*, 2883.

[234] Brauman, J.I.; Blair, L.K. *J. Am. Chem. Soc.* ***1970***, *92*, 5986; Munson, M.S.B. *J. Am.Chem. Soc.* ***1965***, *87*, 2332; Brauman, J.I.; Riveros, J.M.; Blair, L.K. *J. Am. Chem. Soc.* ***1971***, *93*, 3914; Huheey, J.E. *J. Org. Chem.* ***1971***, *36*, 204; Radom, L. *Aust. J. Chem.* ***1975***, *28*, 1; Aitken, E.J.; Bahl, M.K.; Bomben, K.D.; Gimzewski, J.K.; Nolan, G.S.; Thomas, T.D. *J. Am. Chem. Soc.* ***1980***, *102*, 4873.

[235] Taft, R.W.; Taagepera, M.; Abboud J.M.; Wolf, J.F.; Defrees, D.J.; Hehre, W.J.; Bartmess, J.E.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1978***, *100*, 7765. For a scale of polarizability parameters, see Hehre, W.J.; Pau, C.; Headley, A.D.; Taft, R.W.; Topsom, R.D. *J. Am. Chem. Soc.* ***1986***, *108*, 1711.

[236] Bartmess, J.E.; Scott, J.A.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1979***, *101*, 6056.

[237] Bohme, D.K.; Rakshit, A.B.; Mackay, G.I. *J. Am. Chem. Soc.* ***1982***, *104*, 1100.

[238] Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 521; Gerrard, W.; Macklen, E.D. *Chem. Rev.* ***1959***, *59*, 1105. See also Wilson, B.; Georgiadis, R.; Bartmess, J.E. *J. Am. Chem. Soc.* ***1991***, *113*, 1762.

[239] Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 521; p. 529; Hambly, A.N.*Rev. Pure Appl. Chem.* ***1965***, *15*, 87, p. 92.

TABLE 8.7. Thermodynamic Values for the Ionizations of Acetic and Chloroacetic Acids in H_2O at 25°C[238]

		ΔG		ΔH		$T\Delta S$	
Acid	pK_a	kcal mol^{-1}	kJ mol^{-1}	kcal mol^{-1}	kJ mol^{-1}	kcal mol^{-1}	kJ mol^{-1}
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

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.[240] The effect can be extreme: in DMF, picric acid is stronger than HBr,[241] 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^-.[242] 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 8.5 do largely correlate with resonance and field effects), but in general are much weakened, and occasionally reversed.[164]

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[240] For a review, see Parker, A.J. *Q. Rev. Chem. Soc.* ***1962***, *16*, 163.

[241] Sears, P.G.; Wolford, R.K.; Dawson, L.R. *J. Electrochem. Soc.* ***1956***, *103*, 633.

[242] Miller, J.; Parker, A.J. *J. Am. Chem. Soc.* ***1961***, *83*, 117.

CHAPTER 9

Effects of Structure and Medium on Reactivity

When the equation for a reaction of, say, carboxylic acids, is written, it is customary to use the formula RCOOH, which implies that all carboxylic acids undergo the reaction. Since most compounds with a given functional group do give more or less the same reactions, the custom is useful, and the practice is used in this book. It allows a large number of individual reactions to be classified together and serves as an aid both for memory and understanding. Organic chemistry would be a huge morass of unconnected facts without the symbol R. Nevertheless, it must be borne in mind that a given functional group does not always react the same way, regardless of what molecule it is a part of. The reaction at the functional group is influenced by the rest of the molecule. This influence may be great enough to stop the reaction completely or to make it take an entirely different course. Even when two compounds with the same functional group undergo the same reaction, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the structures of the compounds. The greatest variations may be expected when additional functional groups are present.

The effects of structure on reactivity can be divided into three major types: field, resonance (or mesomeric), and steric.[1] In most cases, two or all three of these are operating, and it is usually not easy to tell how much of the rate enhancement (or decrease) is caused by each of the three effects.

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[1] For a monograph, see Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***. For a general theoretical approach to organic reactivity, see Pross, A. *Adv. Phys. Org. Chem.* ***1985***, *21*, 99.

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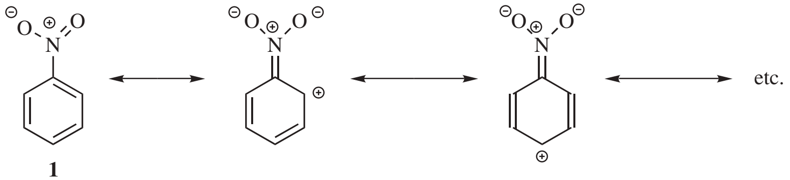
RESONANCE AND FIELD EFFECTS

It is often particularly difficult to separate resonance and field effects; they are frequently grouped together under the heading of *electrical effects*.[2] Field effects were discussed on pp. 19–22. Table 1.3 contains a list of some $+I$ and $-I$ groups. As for resonance effects, on p. 48 it was shown how the electron density distribution in aniline is not the same as it would be if there were no resonance interaction between the ring and the NH_2 group. Most groups that contain an unshared pair on an atom connected to an unsaturated system display a similar effect; that is, the electron density on the group is less than expected, and the density on the unsaturated system is greater. Such groups are said to be electron donating by the resonance effect ($+M$ groups). Alkyl groups, which do not have an unshared pair, are also $+M$ groups, presumably because of hyperconjugation.

On the other hand, groups that have a multiple-bonded electronegative atom directly connected to an unsaturated system are $-M$ groups. In such cases, we can draw canonical forms in which electrons have been taken from the unsaturated system into the group, as in nitrobenzene, **1**. Table 9.1 contains a list of some $+M$ and $-M$ groups.



1

TABLE 9.1. Some Groups with $+M$ and $-M$ Effects, Not Listed in Order of Strength of Effect[a]

$+M$		$-M$	
O^-	SR	NO_2	CHO
S^-	SH	CN	COR
NR_2	Br	COOH	SO_2R
NHR	I	COOR	SO_2OR
NH_2	Cl	$CONH_2$	NO
NHCOR	F	CONHR	Ar
OR	R	$CONR_2$	
OH	Ar		
OCOR			

[a] Ar appears in both lists because it is capable of both kinds of effect.

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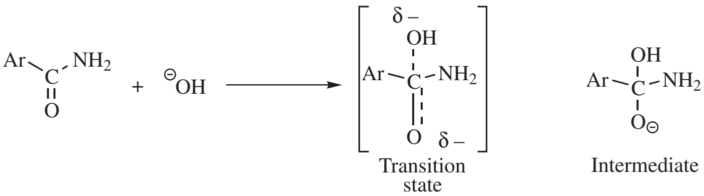
[2] For reviews of the study of electrical effects by ab initio mo methods, see Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 125, *Mol. Struct. Energ.* ***1987***, *4*, 235.

The resonance effect of a group, whether $+M$ or $-M$, operates only when the group is directly connected to an unsaturated system, so that, for example, in explaining the effect of the CH_3O group on the reactivity of the COOH in $CH_3OCH_2CH_2COOH$, only the field effect of the CH_3O need be considered. This is one way of separating the two effects. In *p*-methoxybenzoic acid both effects must be considered. The field effect operates through space, solvent molecules, or the σ bonds of a system, while the resonance effect operates through π electrons.

It must be emphasized once again that neither by the resonance nor by the field effect are any electrons actually being donated or withdrawn, though these terms are convenient (and we will use them). As a result of both effects, the electron-density distribution is not the same as it would be without the effect (see pp. 21, 48). One thing that complicates the study of these effects on the reactivity of compounds is that a given group may have an effect in the transition state that is considerably more or less than it has in the molecule that does not react.

An example will show the nature of electrical effects (resonance and field) on reactivity. In the alkaline hydrolysis of aromatic amides (reaction **16-60**), the rate-determining step is the attack of hydroxide ion at the carbonyl carbon:



2 **3**

In the transition state, which has a structure somewhere between that of the starting amide (**2**) and the intermediate (**3**), the electron density on the carbonyl carbon is increased. Therefore, electron-withdrawing groups ($-I$ or $-M$) on the aromatic ring will lower the free energy of the transition state (by spreading the negative charge). These groups have much less effect on the free energy of **2**. Since G is lowered for the transition state, but not substantially for **2**, $\Delta G^{\ddagger}$ is lowered and the reaction rate is increased (Chapter 6). Conversely, electron-donating groups ($+I$ or $+M$) should decrease the rate of this reaction. Of course, many groups are $-I$ and $+M$, and for these it is not always possible to predict which effect will predominate.

STERIC EFFECTS

It occasionally happens that a reaction proceeds much faster or much slower than expected on the basis of electrical effects alone. In these cases it can often be shown that steric effects are influencing the rate. For example, Table 9.2 lists relative rates for the S_N2 ethanolysis of certain alkyl halides (see p. 426).[3] All these compounds

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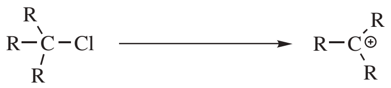
[3] Hughes, E.D. *Q. Rev. Chem. Soc.* ***1948***, *2*, 107.

TABLE 9.2. Relative Rates of Reaction of RBr with Ethanol[3]

R	Relative Rate
CH_3	17.6
CH_3CH_2	1
$CH_3CH_2CH_2$	0.28
$(CH_3)_2CHCH_2$	0.030
$(CH_3)_3CCH_2$	4.2×10^{-6}

are primary bromides; the branching is on the second carbon, so that field-effect differences should be small. As Table 9.2 shows, the rate decreases with increasing β branching and reaches a very low value for neopentyl bromide. This reaction is known to involve an attack by the nucleophile from a position opposite to that of the bromine (see p. 426). The great decrease in rate can be attributed to *steric hindrance*, a sheer physical blockage to the attack of the nucleophile. Another example of steric hindrance is found in 2,6-disubstituted benzoic acids, which are difficult to esterify no matter what the resonance or field effects of the groups in the 2 or the 6 position. Similarly, once 2,6-disubstituted benzoic acids *are* esterified, the esters are difficult to hydrolyze.

Not all steric effects decrease reaction rates. In the hydrolysis of RCl by an S_N1 mechanism (see p. 433), the first step, which is rate determining, involves ionization of the alkyl chloride to a carbocation:



$$R_3C{-}Cl \longrightarrow R_3C^{\oplus}$$

The central carbon in the alkyl chloride is sp^3 hybridized, with angles of ~109.5°, but when it is converted to the carbocation, the hybridization becomes sp^2 and the preferred angle is 120°. If the halide is tertiary and the three alkyl groups are large enough, they will be pushed together by the enforced tetrahedral angle, resulting in strain (see p. 232). This type of strain is called *B strain*[4] (for back strain), and it can be relieved by ionization to the carbocation.[5]

The rate of ionization (and hence the solvolysis rate) of a molecule in which there is B strain is therefore expected to be larger than in cases where B strain is not present. Table 9.3 shows that this is so.[6] Substitution of ethyl groups for the

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[4] For a discussion, see Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 114–121.

[5] For reviews of the effects of strain on reactivity, see Stirling, C.J.M. *Tetrahedron* ***1985***, *41*, 1613; *Pure Appl. Chem.* ***1984***, *56*, 1781.

[6] Brown, H.C.; Fletcher, R.S. *J. Am. Chem. Soc.* ***1949***, *71*, 1845.

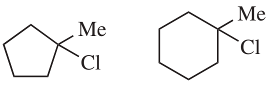
TABLE 9.3. Rates of Hydrolysis of Tertiary Alkyl Chlorides at 25°C in 80% Aqueous Ethanol[6]

Halide	Rate	Halide	Rate
Me_3Cl	0.033	Et_3CCl	0.099
Me_2EtCCl	0.055	$Me_2(i\text{Pr})CCl$	0.029
$MeEt_2CCl$	0.086	$Me(i\text{Pr})_2CCl$	0.45

methyl groups of *tert*-butyl chloride does not cause B strain; the increase in rate is relatively small, and the rate smoothly rises with the increasing number of ethyl groups. The rise is caused by normal field and resonance (hyperconjugation) effects. Substitution by one isopropyl group is not greatly different. But with the second isopropyl group the crowding is now great enough to cause B strain, and the rate is increased 10-fold. Substitution of a third isopropyl group increases the rate still more. Another example where B strain increases solvolysis rates is found with the highly crowded molecules tri-*tert*-butylcarbinol, di-*tert*-butylneopentylcarbinol, *tert*-butyldineopentylcarbinol, and trineopentylcarbinol, where rates of solvolysis of the *p*-nitrobenzoate esters are faster than that of *tert*-butyl nitrobenzoate by factors of 13,000, 19,000, 68,000, and 560, respectively.[7]

Another type of strain, that can affect rates of cyclic compounds, is called *I strain* (internal strain).[8] This type of strain results from changes in ring strain in going from a tetrahedral to a trigonal carbon or vice versa. For example, as mentioned above, S_N1 solvolysis of an alkyl halide involves a change in the bond angle of the central carbon from ~109.5 to ~120°. This change is highly favored in 1-chloro-1-methylcyclopentane because it relieves eclipsing strain (p. 223); thus this compound undergoes solvolysis in 80% ethanol at 25°C, 43.7 times faster

t-BuCl



Relative solvolysis rates 1.0 43.7 0.35

than the reference compound *tert*-butyl chloride.[9] In the corresponding cyclohexyl compound, this factor is absent because the substrate does not have eclipsing strain (p. 223), and this compound undergoes the reaction at about

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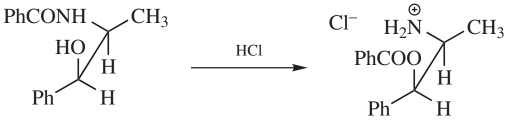
[7] Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421.

[8] For a discussion, see Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 105–107, 126–128.

[9] Brown, H.C.; Borkowski, M. *J. Am. Chem. Soc.* ***1952***, *74*, 1894. See also, Brown, H.C.; Ravindranathan, M.; Peters, E.N.; Rao, C.G.; Rho, M.M. *J. Am. Chem. Soc.* ***1977***, *99*, 5373.

one-third the rate of *tert*-butyl chloride. The reasons for this small decrease in rate are not clear. Corresponding behavior is found in the other direction, in changes from a trigonal to a tetrahedral carbon. Thus cyclohexanone undergoes addition reactions faster than cyclopentanone. Similar considerations apply to larger rings. Rings of 7–11 members exhibit eclipsing and transannular strain; and in these systems reactions in which a tetrahedral carbon becomes trigonal generally proceed faster than in open-chain systems.[10] I-Strain has been shown to be a factor in other reactions as well.[11]

Conformational effects on reactivity can be considered under the heading of steric effects,[12] though in these cases we are considering not the effect of a group X and that of another group X′ upon reactivity at a site Y but the effect of the conformation of the molecule. Many reactions fail entirely unless the molecules are able to assume the proper conformation. An example is the rearrangement of *N*-benzoylnorephedrine. The two diastereomers of this compound behave very differently when treated with alcoholic HCl. In one of the isomers, nitrogen-to-oxygen migration takes place, while the other does not react at all.[13] In order for the migration to take place, the nitrogen must be near the oxygen (*gauche* to it). When **4** assumes this conformation, the methyl and phenyl groups are anti to each other, which is a favorable position, but when **5** has the nitrogen gauche to the oxygen, the methyl must be *gauche* to the phenyl, which is so unfavorable that the reaction does not occur. Other examples are electrophilic additions to C=C double bonds (see p. 999) and E2 elimination reactions (see p. 1478). Also, many examples are known where axial and equatorial groups behave differently.[14]



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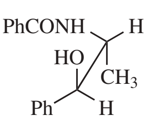

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In steroids and other rigid systems, a functional group in one part of the molecule can strongly affect the rate of a reaction taking place at a remote part of the

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[10] See, for example, Schneider, H.; Thomas, F. *J. Am. Chem. Soc.* ***1980***, *102*, 1424.

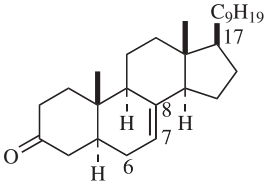
[11] Sands, R.D. *J. Org. Chem.* ***1994***, *59*, 468.

[12] For reviews of conformational effects, see Green, B.S.; Arad-Yellin, R.; Cohen, M.D. *Top. Stereochem.* ***1986***, *16*, 131; Ōki, M. *Acc. Chem. Res.* ***1984***, *17*, 154; Seeman, J.I. *Chem. Rev.* ***1983***, *83*, 83. See also Ōki, M.; Tsukahara, J.; Moriyama, K.; Nakamura, N. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 223, and other papers in this series.

[13] Fodor, G.; Bruckner, V.; Kiss, J.; Óhegyi, G. *J. Org. Chem.* ***1949***, *14*, 337.

[14] For a discussion, see Eliel, E.L. *Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 219–234.

same molecule by altering the conformation of the whole skeleton.



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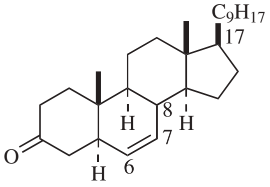

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An example of this effect, called *conformational transmission*, is found in ergost-7-en-3-one (**6**) and cholest-6-en-3-one (**7**), where **7** condenses with benzaldehyde 15 times faster than **6**.[15] The reaction site in both cases is the carbonyl group, and the rate increases because moving the double bond from the 7 to the 6 position causes a change in conformation at the carbonyl group (the difference in the side chain at C-17 does not affect the rate).

QUANTITATIVE TREATMENTS OF THE EFFECT OF STRUCTURE ON REACTIVITY[16]

Suppose a reaction is performed on a substrate molecule that can be represented as XGY, where Y is the site of the reaction, X a variable substituent, and G a skeleton group to which X and Y are attached, and we find that changing X from H to CH_3 results in a rate increase by a factor, say, 10. We would like to know just what part of the increase is due to each of the effects previously mentioned. The obvious way to approach such a problem is to try to find compounds in which one or two of the factors are absent or at least negligible. This is not easy to do acceptably because factors that seem negligible to one investigator do not always appear so to another. The first attempt to give numerical values was that of Hammett.[17] For the cases of

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[15] Barton, D.H.R.; McCapra, F.; May, P.J.; Thudium, F. *J. Chem. Soc.* ***1960***, 1297.

[16] For monographs, see Exner, O. *Correlation Analysis of Chemical Data*, Plenum, NY, ***1988***; Johnson, C.D. *The Hammett Equation*, Cambridge University Press, Cambridge, ***1973***; Shorter, J. *Correlation Analysis of Organic Reactivity*, Wiley, NY, ***1982***, *Correlation Analysis in Organic Chemistry*, Clarendon, N.B. Press, Oxford, ***1973***; Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, *Advances in Linear Free Energy Relationships*, Plenum, NY, ***1972***; Wells, P.R. *Linear Free Energy Relationships*, Academic Press, NY, ***1968***. For reviews, see Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 311–383; Lewis, E.S., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions* (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), 4th ed., Wiley, NY, ***1986***, pp. 871–901; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press: Cambridge, ***1984***, pp. 38–68; Charton, M. *CHEMTECH* ***1974***, 502, **1975**, 245; Hine, J. *Structural Effects in Organic Chemistry*, Wiley, NY, ***1975***, pp. 55–102; Afanas'ev, I.B. *Russ. Chem. Rev.* ***1971***, *40*, 216; Laurence, C.; Wojtkowiak, B. *Ann. Chim.* (*Paris*) ***1970***, [*14*] *5*, 163. For a historical perspective, see Grunwald, E. *CHEMTECH* ***1984***, 698.

[17] For a review, see Jaffé, H.H. *Chem. Rev.* ***1953***, *53*, 191.

m- and *p*-XC_6H_4Y, Hammett set up the equation

$$\log \frac{k}{k_0} = \sigma\rho$$

where k_0 is the rate constant or equilibrium constant for $X = H$, k is the constant for the group X, ρ is a constant for a given reaction under a given set of conditions, and σ is a constant characteristic of the group X. The equation is called the *Hammett equation*.

The value of ρ was set at 1.00 for ionization of XC_6H_4COOH in water at 25°C. The values of σ_m and σ_p were then calculated for each group (for a group X, σ is different for the meta and para positions). Once a set of σ values was obtained, ρ values could be obtained for other reactions from the rates of just two X-substituted compounds, if the σ values of the X groups were known (in practice, at least four well-spaced values are used to calculate ρ because of experimental error and because the treatment is not exact). With the ρ value thus calculated and the known σ values for other groups, rates can be predicted for reactions that have not yet been run.

The σ values are numbers that sum up the total electrical effects (resonance plus field) of a group X when attached to a benzene ring. The treatment usually fails for the ortho position. The Hammett treatment has been applied to many reactions and to many functional groups and correlates quite well an enormous amount of data. Jaffé's review article[17] lists ρ values for 204 reactions,[18] many of which have different ρ values for different conditions. Among them are reactions as disparate as the following:

Rate constants for

$$\mathrm{ArCOOMe} + \mathrm{OH^-} \longrightarrow \mathrm{ArCOO^-}$$

$$\mathrm{ArCH_2Cl} + \mathrm{I^-} \longrightarrow \mathrm{ArCH_2I}$$

$$\mathrm{ArNH_2} + \mathrm{PhCOCl} \longrightarrow \mathrm{ArNHCOPh}$$

$$\mathrm{ArH} + \mathrm{NO_2^+} \longrightarrow \mathrm{ArNO_2}$$

$$\mathrm{ArCO_2OCMe_3} \longrightarrow \text{Decomposition (a free-radical process)}$$

Equilibrium constants for

$$\mathrm{ArCOOH} + \mathrm{H_2O} \rightleftharpoons \mathrm{ArCOO^-} + \mathrm{H_3O^+}$$

$$\mathrm{ArCHO} + \mathrm{HCN} \rightleftharpoons \mathrm{ArCH(CN)OH}$$

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[18] Additional ρ values are given in Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171 and van Bekkum, H.; Verkade, P.E.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1959***, *78*, 821.

The Hammett equation has also been shown to apply to many physical measurements, including ir frequencies and nmr chemical shifts.[19] The treatment is reasonably successful whether the substrates are attacked by electrophilic, nucleophilic, or free-radical reagents, the important thing being that the mechanism be the same *within* a given reaction series.

However, there are many reactions that do not fit the treatment. These are mostly reactions where the attack is directly on the ring and where the X group can enter into direct resonance interaction with the reaction site in the transition state (i.e., the substrate is XY rather than XGY). For these cases, two new sets of σ values have been devised: σ^+ values (proposed by H.C. Brown) for cases in which an electron-donating group interacts with a developing positive charge in the transition state (this includes the important case of electrophilic aromatic substitutions; see Chapter 11), and σ values, where electron-withdrawing groups interact with a developing negative charge. Table 9.4 gives σ, σ^+, and σ^- values for some common X groups.[20] As shown in the table, σ is not very different from σ^+ for most electron-withdrawing groups. The values of σ_m^- are not shown in Table 9.4, since they are essentially the same as the σ_m values.

A positive value of σ indicates an electron-withdrawing group and a negative value an electron-donating group.[21] The constant ρ measures the susceptibility of the reaction to electrical effects.[22] Reactions with a positive ρ are helped by electron-withdrawing groups and vice versa. The following ρ values for the ionization of some carboxylic acids illustrate this:[23]

$XC_6H_4{-}COOH$	1.00	$XC_6H_4{-}CH{=}CH{-}COOH$	0.47
$XC_6H_4{-}CH_2{-}COOH$	0.49	$XC_6H_4{-}CH_2CH_2{-}COOH$	0.21

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[19] For a review of Hammett treatment of nmr chemical shifts, see Ewing, D.F., in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 357–396.

[20] Unless otherwise noted, σ values are from Exner, O. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 439–540, and σ^+ values from Okamoto,Y.; Inukai, T.; Brown, H.C. *J. Am. Chem. Soc.* ***1958***, *80*, 4969 and Brown, H.C.; Okamoto,Y. *J. Am. Chem. Soc.* ***1958***, *80*, 4979. σ^- values, except as noted, are from Jaffé, H.H. *Chem. Rev.* ***1953***, *53*, 191. Exner, O. pp. 439–540, has extensive tables giving values for >500 groups, as well as σ^+, σ^-, σ_I, σ_R^0, and E_s values for many of these groups. Other large tables of the various sigma values are found in Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* ***1991***, *91*, 165. For tables of σ_p, σ_m, σ^+, σ_I, and σ_R^0 values of many groups containing Si, Ge, Sn, and Pb atoms, see Egorochkin, A.N.; Razuvaev, G.A. *Russ. Chem. Rev.* ***1987***, *56*, 846. For values for heteroaromatic groups, see Mamaev, V.P.; Shkurko, O.P.; Baram, S.G. *Adv. Heterocycl. Chem.* ***1987***, *42*, 1.

[21] For discussions of the precise significance of σ, see Dubois, J.E.; Ruasse, M.; Argile, A. *J. Am. Chem. Soc.* ***1984***, *106*, 4840; Ruasse, M.; Argile, A.; Dubois, J.E. *J. Am. Chem. Soc.* ***1984***, *106*, 4846; Lee, I.; Shim, C.S.; Chung, S.Y.; Kim, H.Y.; Lee, H.W. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1919.

[22] Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877.

[23] Binev, I.G.; Kuzmanova, R.B.; Kaneti, J.; Juchnovski, I.N. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1533.

TABLE 9.4. The σ, σ^+, and σ^- Values for Some Common Groups[20]

Group	σ_p	σ_m	σ_p^+	σ_m^+	σ_p^-
O^-	-0.81[24]	-0.47[24]	-4.27[25]	-1.15[25]	
NMe_2	-0.63	10.10	-1.7		
NH_2	-0.57	-0.09	-1.3	-0.16	
OH	-0.38[26]	0.13[26]	-0.92[27]		
OMe	-0.28[26]	0.10	-0.78	0.05	
CMe_3	-0.15	-0.09	-0.26	-0.06	
Me	-0.14	-0.06	-0.31	-0.10[28]	
H	0	0	0	0	0
Ph	0.05[29]	0.05	-0.18	0[29]	
COO^-	0.11[24]	0.02[24]	-0.41[25]	-0.10[25]	
F	0.15	0.34	-0.07	0.35	
Cl	0.24	0.37	0.11	0.40	
Br	0.26	0.37	0.15	0.41	
I	0.28[29]	0.34	0.14	0.36	
N=NPh[30]	0.34	0.28	0.17		
COOH[31]	0.44	0.35	0.42	0.32	0.73
COOR	0.44	0.35	0.48	0.37	0.68
COMe	0.47	0.36			0.87
CF_3	0.53	0.46		0.57[28]	
NH_3^+	0.60[25]	0.86[26]			
CN[32]	0.70	0.62	0.66	0.56	1.00
SO_2Me	0.73	0.64			
NO_2	0.81	0.71	0.79	0.73[28]	1.27
NMe_3^+	0.82[33]	0.88[33]	0.41	0.36	
N_2^+	1.93[34]	1.65[34]	1.88[34]		3[35]

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[24] Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, p. 42.

[25] See Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877.

[26] Matsui, T.; Ko, H.C.; Hepler, L.G. *Can. J. Chem.* ***1974***, *52*, 2906.

[27] de la Mare, P.B.D.; Newman, P.A. *Tetrahedron Lett.* ***1982***, *23*, 1305 give this value as −1.6.

[28] Amin, H.B.; Taylor, R. *Tetrahedron Lett.* ***1978***, 267.

[29] Sjöström, M.; Wold, S. *Chem. Scr.* ***1976***, *9*, 200.

[30] Byrne, C.J.; Happer, D.A.R.; Hartshorn, M.P.; Powell, H.K.J. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1649.

[31] For a review of directing and activating effects of C=O, C=C, C=N, and C=S groups, see Charton, M., in Patai, S. *The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 239–298.

[32] For a review of directing and activating effects of C≡N and C≡C groups, see Charton, M., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 269–323.

[33] McDaniel, D.H.; Brown, H.C. *J. Org. Chem.* ***1958***, *23*, 420.

[34] Ustynyuk, Yu. A.; Subbotin, O.A.; Buchneva, L.M.; Gruzdneva, V.N.; Kazitsyna, L.A. *Doklad. Chem.* ***1976***, *227*, 175.

[35] Lewis, E.S.; Johnson, M.D. *J. Am. Chem. Soc.* ***1959***, *81*, 2070.

This example shows that the insertion of a CH_2 or a CH=CH group diminishes electrical effects to about the same extent, while a CH_2CH_2 group diminishes them much more. A $\rho > 1$ would mean that the reaction is more sensitive to electrical effects than is the ionization of XC_6H_4COOH ($\rho = 1.00$).

Similar calculations have been made for compounds with two groups X and X′ on one ring, where the σ values are sometimes additive and sometimes not,[36] for other ring systems, such as naphthalene[37] and heterocyclic rings,[38] and for ethylenic and acetylenic systems.[39]

The Hammett equation is a *linear free-energy relationship* (*LFER*). This can be demonstrated as follows for the case of equilibrium constants (for rate constants a similar demonstration can be made with $\Delta G^{\ddagger}$ instead of ΔG). For each reaction, where X is any group,

$$\Delta G = -RT \ln K$$

For the unsubstituted case,

$$\Delta G_0 = -RT \ln K_0$$

The Hammett equation can be rewritten

$$\log K - \log K_0 = \sigma\rho$$

so that

$$\frac{-\Delta G}{2.3RT} + \frac{\Delta G_0}{2.3RT} = \sigma\rho$$

and

$$-\Delta G = \sigma\rho 2.3RT - \Delta G_0$$

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[36] Stone, R.M.; Pearson, D.E. *J. Org. Chem.* ***1961***, *26*, 257.

[37] Berliner, E.; Winikov, E.H. *J. Am. Chem. Soc.* ***1959***, *81*, 1630; see also, Well, P.R.; Ehrenson, S.; Taft, R.W. *Prog. Phys.Org. Chem.* ***1968***, *6*, 147.

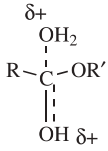
[38] For reviews, see Charton, M. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 175–268; Tomasik, P.; Johnson, C.D. *Adv. Heterocycl. Chem.* ***1976***, *20*, 1.

[39] For reviews of the application of the Hammett treatment to unsaturated systems, see Ford, G.P.; Katritzky, A.R.; Topsom, R.D., in *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 269–311; Charton, M. *Prog. Phys. Org. Chem.* ***1973***, *10*, 81.

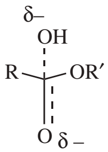
For a given reaction under a given set of conditions, σ, R, T, and ΔG_0 are all constant, so that σ is linear with ΔG.

The Hammett equation is not the only LFER.[40] Some, like the Hammett equation, correlate structural changes in reactants, but the Grunwald–Winstein relationship (see p. 505) correlates changes in solvent and the Brønsted relation (see p. 373) relates acidity to catalysis. The Taft equation is a structure-reactivity equation that correlates only field effects.[41]

Taft, following Ingold,[42] assumed that for the hydrolysis of carboxylic esters, steric and resonance effects will be the same whether the hydrolysis is catalyzed by acid or base (see the discussion of ester-hydrolysis mechanisms, reaction **16-59**). Rate differences would therefore be caused only by the field effects of R and R′ in RCOOR′. This is presumably a good system to use for this purpose because the transition state for acid-catalyzed hydrolysis (**8**) has a greater positive charge (and is hence destabilized by $-I$ and stabilized by $+I$ substituents) than the starting ester, while the transition state for base-catalyzed hydrolysis (**9**) has a greater negative charge than the starting ester. Field effects of substituents X could therefore be determined by measuring the rates of acid- and base-catalyzed hydrolysis of a series XCH_2COOR',[43] where R′ is held constant.[38] From these rate constants, a value σ_I could be determined by the equation[44]



8



9

$$\sigma_I + 0.181\left[\log\left(\frac{k}{k_0}\right)_{\mathrm{B}} - \log\left(\frac{k}{k_0}\right)_{\mathrm{A}}\right]$$

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[40] For a discussion of physicochemical preconditions for LFERs, see Exner, O. *Prog. Phys. Org. Chem.* ***1990***, *18*, 129.

[41] For reviews of the separation of resonance and field effects, see Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119; Shorter, J. *Q. Rev. Chem. Soc.* ***1970***, *24*, 433; *Chem. Ber.* ***1969***, *5*, 269. For a review of field and inductive effects, see Reynolds, W.F. *Prog. Phys. Org. Chem.* ***1983***, *14*, 165. For a review of field effects on reactivity, see Grob, C.A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 569.

[42] Ingold, C.K. *J. Chem. Soc.* ***1930***, 1032.

[43] For another set of field-effect constants, based on a different premise, see Draffehn, J.; Ponsold, K. *J. Prakt. Chem.* ***1978***, *320*, 249.

[44] The symbol σ_F is also used in the literature; sometimes in place of σ_I, and sometimes to indicate only the field (not the inductive) portion of the total effect (p. 19).

In this equation $(k/k_0)_\mathrm{B}$ is the rate constant for basic hydrolysis of XCH_2COOR' divided by the rate constant for basic hydrolysis of CH_3COOR', $(k/k_0)_\mathrm{A}$ is the similar rate-constant ratio for acid catalysis, and 0.181 is an arbitrary constant. σ_I is a substituent constant for a group X, substituted at a saturated carbon, that reflects only field effects.[45] Once a set of σ_I values was obtained, it was found that the equation

$$\sigma_I + 0.181\left[\log\left(\frac{k}{k_0}\right)_\mathrm{B} - \log\left(\frac{k}{k_0}\right)_\mathrm{A}\right]$$

holds for a number of reactions, among them:[46]

$$RCH_2OH \longrightarrow RCH_2O^-$$

$$RCH_2Br + PhS^- \longrightarrow RCH_2SPh + Br^-$$

$$\text{Acetone} + I_2\text{, catalyzed by } RCOOH \longrightarrow$$

$$o\text{-Substituted-}ArNH_2 + PhCOCl \longrightarrow ArNHCOPh$$

As with the Hammett equation, σ_I is constant for a given reaction under a given set of conditions. For very large groups the relationship may fail because of the presence of steric effects, which are not constant. The equation also fails when X enters into resonance with the reaction center to different extents in the initial and transition states. A list of some σ_I values is given in Table 9.5.[47] The σ_I values are about what we would expect for pure field-effect values (see p. 21) and are additive, as field effects (but not resonance or steric effects) would be expected to be. Thus, in moving a group one carbon down the chain, there is a decrease by a factor of 2.8 ± 0.5 (cf. the values of R and RCH_2 in Table 9.5 for R $=$ Ph and CH_3CO). An inspection of Table 9.5 shows that σ_I values for most groups are fairly close to the σ_m values (Table 9.4) for the same groups. This is not surprising, since σ_m values would be expected to arise almost entirely from field effects, with little contribution from resonance.

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[45] There is another set of values (called σ^* values) that are also used to correlate field effects. These are related to σ_I values by $= \sigma_I(X) = 0.45\sigma$. We discuss only σ_I, and not σ^* values.

[46] Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171, p. 196.

[47] These values are from Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* ***1979***, *44*, 4766, except that the values for NHAc, OH, and I are from Wells, P.R.; Ehrenson, S.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1968***, *6*, 147, the values for Ph and NMe_3^+ are from Taft, R.W.; Ehrenson, S.; Lewis, I.C.; Glick, R. *J. Am.Chem. Soc.* ***1959***, *81*, 5352 and Taft, R.W.; Deno, N.C.; Skell, P.S. *Annu. Rev. Phys. Chem.* ***1958***, *8*, 287, and the value for CMe_3 is from Seth-Paul, W.A.; de Meyer-van Duyse, A.; Tollenaere, J.P. *J. Mol. Struct.* ***1973***, *19*, 811. The values for the CH_2Ph and CH_2COCH_3 groups were calculated from σ^* values by the formula given in reference 45. For much larger tables of σ_I and σ_R values, see Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119. See also Ref. 20 and Taylor, P.J.; Wait, A.R. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1765.

TABLE 9.5. The σ_I and σ_R^0 Values for Some Groups[47]

Group	σ_I	σ_R^0	Group	σ_I	σ_R^0
CMe_3	−0.07	−0.17	OMe	0.27	−0.42
Me	−0.05	−0.13	OH	0.27	−0.44
H	0	0	I	0.39	−0.12
$PhCH_2$	0.04		CF_3	0.42	0.08
NMe_2[48]	0.06	−0.55	Br	0.44	−0.16
Ph	0.10	−0.10	Cl	0.46	−0.18
CH_3COCH_2	0.10		F	0.50	−0.31
NH_2	0.12	−0.50	CN	0.56	0.08
CH_3CO	0.20	0.16	SO_2Me	0.60	0.12
COOEt	0.20	0.16	NO_2	0.65	0.15
NHAc	0.26	−0.22	NMe_3[49]	0.86	

Since σ_p values represent the sum of resonance and field effects, these values can be divided into resonance and field contributions if σ_I is taken to represent the field-effect portion.[50] The resonance contribution σ_R[51] is defined as

$$\sigma_R = \sigma_p - \sigma_I$$

As it stands, however, this equation is not very useful because the σ_R value for a given group, which should be constant if the equation is to have any meaning, is actually not constant but depends on the nature of the reaction.[52] In this respect, the σ_I values are much better. Although they vary with solvent in some cases, σ_I values are essentially invariant throughout a wide variety of reaction series. However, it is possible to overcome[53] the problem of varying σ_R values by using a special set of σ_R values, called

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[48] For σ_R^0 values for some other NR_2 groups, see Korzhenevskaya, N.G.; Titov, E.V.; Chotii, K.Yu.; Chekhuta, V.G. *J. Org. Chem. USSR* ***1987***, *28*, 1109.

[49] Although we give a σ_I value for NMe_3^+, (and *F* values for three charged groups in Table 9.6), it has been shown that charged groups (called polar substituents) cannot be included with uncharged groups (dipolar substituents) in one general scale of electrical substituent effects: Marriott, S.; Reynolds, J.D.; Topsom, R.D. *J. Org. Chem.* ***1985***, *50*, 741.

[50] Roberts, J.D.; Moreland, Jr., W.T. *J. Am. Chem. Soc.* ***1953***, *75*, 2167; Taft, R.W. *J. Am. Chem. Soc.* ***1957***, *79*, 1045; *J. Phys. Chem.* ***1960***, *64*, 1805; Taft, R.W.; Lewis, I.C. *J. Am. Chem. Soc.* ***1958***, *80*, 2436; Taft, R.W.; Deno, N.C.; Skell, P.S. *Annu. Rev. Phys. Chem.* ***1958***, *9*, 287, see pp. 290–293.

[51] For reviews of the σ_I and σ_R concept as applied to benzenes and naphthalenes, respectively, see Ehrenson, S.; Brownlee, R.T.C.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1973***, *10*, 1. See also, Taft, R.W.; Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 1; Charton, M. *Prog. Phys. Org. Chem.* ***1987***, *16*, 287.

[52] Taft, R.W.; Lewis, I.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5343; Reynolds, W.F.; Dais, P.; MacIntyre, D.W.; Topsom, R.D.; Marriott, S.; von Nagy-Felsobuki, E.; Taft, R.W. *J. Am. Chem. Soc.* ***1983***, *105*, 378.

[53] For a different way of overcoming this problem, see Happer, D.A.R.; Wright, G.J. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 694.

σ_R^{o},[54] that measure the ability to delocalize π electrons into or out of an unperturbed or "neutral" benzene ring. Several σ_R^{o} scales have been reported; the most satisfactory values are obtained from ^{13}C chemical shifts of substituted benzenes.[55] Table 9.5 lists some values of σ_R^{o}, most of which were obtained in this way.[56]

An equation such as

$$\log \frac{k}{k_0} = \rho_I \sigma_I + \rho_R \sigma_R^{\mathrm{o}}$$

which treats resonance and field effects separately, is known as a *dual substituent parameter equation*.[57]

The only groups in Table 9.5 with negative values of σ_I are the alkyl groups methyl and *t*-butyl. There has been some controversy on this point.[58] One opinion is that σ_I values decrease in the series methyl, ethyl, isopropyl, *tert*-butyl (respectively, −0.046, −0.057, −0.065, −0.074).[59] Other evidence, however, has led to the belief that all alkyl groups have approximately the same field effect and that the σ_I values are invalid as a measure of the intrinsic field effects of alkyl groups.[60]

Another attempt to divide σ values into resonance and field contributions[61] is that of Swain and Lupton, who have shown that the large number of sets of σ values (σ_m, σ_p, σ_p^-, σ_p^+, σ_I, σ_R^{o}, etc., as well as others we have not mentioned) are not entirely independent and that linear combinations of two sets of new values F (which expresses the field-effect contribution) and R (the resonance contribution) satisfactorily express 43 sets of values.[62] Each set is expressed as

$$\sigma = fF + rR$$

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[54] Taft, R.W.; Ehrenson, S.; Lewis, I.C.; Glick, R.E. *J. Am. Chem. Soc.* ***1959***, *81*, 5352.

[55] Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* ***1979***, *44*, 4766. See also, Marriott, S.; Topsom, R.D. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1045.

[56] For a set of σ_R values for use in XY$^+$ systems, see Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271.

[57] There are also three-parameter equations. See, for example, de Ligny, C.L.; van Houwelingen, H.C. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 559.

[58] For a discussion, see Shorter, J. in Chapman, N.B.; Shorter, J. *Advances in Linear Free Energy Relationships*, Plenum, NY, ***1972***, pp. 98–103.

[59] For support for this point of view, see Levitt, L.S.; Widing, H.F. *Prog. Phys. Org. Chem.* ***1976***, *12*, 119; Taft, R.W.; Levitt, L.S. *J. Org. Chem.* ***1977***, *42*, 916; MacPhee, J.A.; Dubois, J.E. *Tetrahedron Lett.* ***1978***, 2225; Screttas, C.G. *J. Org. Chem.* ***1979***, *44*, 3332; Hanson, P. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 101.

[60] For support for this point of view, see, for example, Ritchie, C.D. *J. Phys. Chem.* ***1961***, *65*, 2091; Bordwell, F.G.; Drucker, G.E.; McCollum, G.J. *J. Org. Chem.* ***1976***, *41*, 2786; Bordwell, F.G.; Fried, H.E. *Tetrahedron Lett.* ***1977***, 1121; Charton, M. *J. Am. Chem. Soc.* ***1977***, *99*, 5687; *J. Org. Chem.* ***1979***, *44*, 903; Adcock, W.; Khor, T. *J. Org. Chem.* ***1978***, *43*, 1272; DeTar, D.F. *J. Org. Chem.* ***1980***, *45*, 5166; *J. Am. Chem. Soc.* ***1980***, *102*, 7988.

[61] Yukawa and Tsuno have still another approach, also involving dual parameters: Yukawa, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1959***, *32*, 971. For a review and critique of this method, see Shorter, J., in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 119–173, 126–144. This article also discusses the Swain–Lupton and Taft σ_I, σ_R approaches. For yet other approaches, see Afanas'ev, I.B. *J. Org. Chem. USSR* ***1981***, *17*, 373; *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1589; Ponec, R. *Coll. Czech. Chem. Commun.* ***1983***, *48*, 1564.

[62] Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* ***1983***, *105*, 492 and references cited therein.

TABLE 9.6. The *F* and *R* Values for Some Groups[63]

Group	*F*	*R*	Group	*F*	*R*
COO^-	−0.27	0.40	OMe	0.54	−1.68
Me_3C	−0.11	−0.29	CF_3	0.64	0.76
Et	−0.02	−0.44	I	0.65	−0.12
Me	−0.01	−0.41	Br	0.72	−0.18
H	0	0	Cl	0.72	−0.24
Ph	0.25	−0.37	F	0.74	−0.60
NH_2	0.38	−2.52	$NHCOCH_3$	0.77	−1.43
COOH	0.44	0.66	CN	0.90	0.71
OH	0.46	−1.89	NMe_3^+	1.54	
COOEt	0.47	0.67	N_2^+	2.36	2.81
$COCH_3$	0.50	0.90			

where f and r are weighting factors. Some F and R values for common groups are given in Table 9.6.[63] From the calculated values of f and r, Swain and Lupton calculated that the importance of resonance, % R, is 20% for σ_m, 38% for σ_p, and 62% for σ_p^+.[64] This is another dual substituent parameter approach.

Taft was also able to isolate steric effects.[65] For the acid-catalyzed hydrolysis of esters in aqueous acetone, long (k/k_0) was shown to be insensitive to polar effects.[66] In cases where resonance interaction was absent, this value was proportional only to steric effects (and any others[67] that are not field or resonance). The equation is

$$\log \frac{k}{k_0} = E_S$$

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[63] Taken from a much longer list in Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* ***1983***, *105*, 492. Long tables of *R* and *F* values are also given in Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* ***1991***, *91*, 165.

[64] The Swain–Lupton treatment has been criticized by Reynolds, W.F.; Topsom, R.D. *J. Org. Chem.* ***1984***, *49*, 1989; Hoefnagel, A.J.; Oosterbeek, W.; Wepster, B.M. *J. Org. Chem.* ***1984***, *49*, 1993; and Charton, M. *J. Org. Chem.* ***1984***, *49*, 1997. For a reply to these criticisms, see Swain, C.G. *J. Org. Chem.* ***1984***, *49*, 2005. A study of the rates of dediazoniation reactions (**13-32**) was more in accord with the Taft and Charton (see Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119) σ_I and σ_R values than with the Swain–Lupton *F* and *R* values: Nakazumi, H.; Kitao, T.; Zollinger, H. *J. Org. Chem.* ***1987***, *52*, 2825.

[65] For reviews of quantitative treatments of steric effects, see Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* ***1988***, *43*, 173; Gallo, R. *Prog. Phys. Org. Chem.* ***1983***, *14*, 115; Unger, S.H.; Hansch, C. *Prog. Phys. Org. Chem.* ***1976***, *12*, 91.

[66] Another reaction used for the quantitative measurement of steric effects is the aminolysis of esters (**16-75**); De Tar, D.F.; Delahunty, C. *J. Am. Chem. Soc.* ***1983***, *105*, 2734.

[67] It has been shown that E_s values include solvation effects: McClelland, R.A.; Steenken, S. *J. Am. Chem. Soc.* ***1988***, *110*, 5860.

TABLE 9.7. The E_s, υ, and V^a Values for Some Groups[68]

Group	E_s	υ	$V^a \times 10^2$	Group	E_s	υ	$V^a \times 10^2$
H	0	0		Cyclohexyl	−2.03	0.87	6.25
F	−0.46	0.27	1.22	*i*-Bu	−2.17	0.98	5.26
CN	−0.51			*sec*-Bu	−2.37	1.02	6.21
OH	−0.55			CF_3	−2.4	0.91	3.54
OMe	−0.55		3.39	*t*-Bu	−2.78	1.24	7.16
NH_2	−0.61			NMe_3^+	−2.84		
Cl	−0.97	0.55	2.54	Neopentyl	−2.98	1.34	5.75
Me	−1.24	0.52	2.84	CCl_3	−3.3	1.38	6.43
Et	−1.31	0.56	4.31	CBr_3	−3.67	1.56	7.29
I	−1.4	0.78	4.08	$(Me_3CCH_2)_2CH$	−4.42	2.03	
Pr	−1.6	0.68	4.78	Et_3C	−5.04	2.38	
*i*Pr	−1.71	0.76	5.74	Ph_3C	−5.92	2.92	

Some E_s values are given in Table 9.7,[68] where hydrogen is taken as standard, with a value of 0.[69] This treatment is more restricted than those previously discussed, since it requires more assumptions, but the E_s values are approximately in order of the size of the groups. Charton has shown that E_s values for substituents of types CH_2X, CHX_2, and CX_3 are linear functions of the van der Waals radii for these groups.[70]

Two other steric parameters are independent of any kinetic data. Charton's v values are derived from van der Waals radii,[71] and Meyer's V^a values from the volume of the portion of the substituent that is within 0.3 nm of the reaction center.[72] The V^a values are obtained by molecular mechanics calculations based on the structure of the molecule. Table 9.7 gives υ and V^a values for some groups.[73] As can be seen in the table, there is a fair, but not perfect, correlation among the E_s, υ, and V^a values. Other sets of steric values, for example, E_s'[74] E_s^*,[75] Ω_s,[76] and f,[77] have also been proposed.[73]

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[68] The E_s, v, and V^a values are taken from longer tables in, respectively, Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* ***1988***, *43*, 173; Gallo, R. *Prog. Phys. Org. Chem.* ***1983***, *14*, 115; Unger, S.H.; Hansch, C. *Prog. Phys. Org. Chem.* ***1976***, *12*, 91. Charton, M. *J. Am. Chem. Soc.* ***1975***, *97*, 1552; *J. Org. Chem.* ***1976***, *41*, 2217; and Meyer, A.Y. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1567.

[69] In Taft's original work, Me was given the value 0. The E_s values in Table 9.7 can be converted to the orginal values by adding 1.24.

[70] Charton, M. *J. Am. Chem. Soc.* ***1969***, *91*, 615.

[71] Charton, M. *J. Am. Chem. Soc.* ***1975***, *97*, 1552; *J. Org. Chem.* ***1976***, *41*, 2217. See also, Charton, M. *J. Org. Chem.* ***1978***, *43*, 3995; Idoux, J.P.; Schreck, J.O. *J. Org. Chem.* ***1978***, *43*, 4002.

[72] Meyer, A.Y. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1567.

[73] For a discussion of the various steric parameters, see DeTar, D.F. *J. Org. Chem.* ***1980***, *45*, 5166; *J. Am. Chem. Soc.* ***1980***, *102*, 7988.

[74] MacPhee, J.A.; Panaye, A.; Dubois, J.E. *J. Org. Chem.* ***1980***, *45*, 1164; Dubois, J.E.; MacPhee, J.A.; Panaye, A. *Tetrahedron* ***1980***, *36*, 919. See also, Datta, D.; Sharma, G.T. *J. Chem. Res. (S)* ***1987***, 422.

[75] Fellous, R.; Luft, R. *J. Am. Chem. Soc.* ***1973***, *95*, 5593.

[76] Komatsuzaki, T.; Sakakibara, K.; Hirota, M. *Tetrahedron Lett.* ***1989***, *30*, 3309; *Chem. Lett.* ***1990***, 1913.

[77] Beckhaus, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 593.

Since the Hammett equation has been so successful in the treatment of the effects of groups in the meta and para positions, it is not surprising that attempts have been made to apply it to ortho positions also.[78] The effect on a reaction rate or equilibrium constant of a group in the ortho position is called the *ortho effect*.[79] Despite the many attempts made to quantify ortho effects, no set of values has so far commanded general agreement. However, the Hammett treatment is successful for ortho compounds when the group Y in *o*-XC_6H_4Y is separated from the ring; for example, ionization constants of *o*-$XC_6H_4OCH_2COOH$ can be successfully correlated.[80]

Linear free-energy relationships can have mechanistic implications. If log (k/k_0) is linear with the appropriate σ, it is likely that the same mechanism operates throughout the series. If not, a smooth curve usually indicates a gradual change in mechanism, while a pair of intersecting straight lines indicates an abrupt change,[81] though nonlinear plots can also be due to other causes, such as complications arising from side reactions. If a reaction series follows σ^+ or σ^- better than σ it generally means that there is extensive resonance interaction in the transition state.[82]

Information can also be obtained from the magnitude and sign of ρ. For example, a strongly negative ρ value indicates a large electron demand at the reaction center, from which it may be concluded that a highly electron-deficient center, perhaps an incipient carbocation, is involved. Conversely, a positive ρ value is associated with a developing negative charge in the transition state.[83] The $\sigma\rho$ relationship even applies to free-radical reactions, because free radicals can have some polar character (p. 939), though ρ values here are usually small (less than ~1.5) whether positive or negative. Reactions involving cyclic transition states (p. 297) also exhibit very small ρ values.

EFFECT OF MEDIUM ON REACTIVITY AND RATE

There is no question that the solvent chosen for a given reaction has a profound influence on the course of that reaction. Protic versus aprotic solvents as well as polar versus nonpolar solvents can have effects ranging from solubility to solvent assisted ionization or stabilization of transition states. Reactions can

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[78] For reviews, see Fujita, T.; Nishioka, T. *Prog. Phys. Org. Chem.* ***1976***, *12*, 49; Charton, M. *Prog. Phys. Org. Chem.* ***1971***, *8*, 235; Shorter, J., in Chapman, N.B.; Shorter, J. *Advances in Linear Free Energy Relaltionships*, Plenum, NY, ***1972***, pp. 103–110. See also, Segura, P. *J. Org. Chem.* ***1985***, *50*, 1045; Robinson, C.N.; Horton, J.L.; Fosheé, D.O.; Jones, J.W.; Hanissian, S.H.; Slater, C.D. *J. Org. Chem.* ***1986***, *51*, 3535.

[79] This is not the same as the ortho effect discussed on p. $$$.

[80] Charton, M. *Can. J. Chem.* ***1960***, *38*, 2493.

[81] For a discussion, see Schreck, J.O. *J. Chem. Educ.* ***1971***, *48*, 103.

[82] See, however, Gawley, R.E. *J. Org. Chem.* ***1981***, *46*, 4595.

[83] For another method of determining transition state charge, see Williams, A. *Acc. Chem. Res.* ***1984***, *17*, 425.

also be done neat in one of the reactants, in the gas phase, on solid support or in the solid phase. Environmental friendly chemistry (green chemistry) is becoming increasingly important, and chemical reactions in nonpolluting (often non-organic) solvents is of particular interest.[84] This section will describe alternative reaction media as well as other medium-related things that influence chemical reactions.

HIGH PRESSURE

Acceleration of some chemical reactions is possible when high-pressure techniques are employed.[85,86] The effects on a given reaction can be predicted to a certain extent because the thermodynamic properties of solutions are well known. The rate of a reaction can be expressed in terms of the activation volume, $\Delta V^{\ddagger}$

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta V^{\ddagger}}{RT}$$

so rate constants vary with pressure.[86] "The activation volume[87] is the difference in partial molal volume between the transition state and the initial state. From a synthetic point of view this could be approximated by the molar volume."[86] If the volume of activation is negative, the rate of the reaction will be accelerated by increasing pressure. As the pressure increases, the value of $\Delta V^{\ddagger}$ decreases and the system does not strictly obey equation (11.4) > 10 kbar (1 bar $= 0.986924$ atm $= 1.1019716\,\text{kg cm}^{-2}$). If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. Cleavage of a bond, dispersal of charge, or neutralization of the transition state and diffusion control lead to a positive volume of activation. Matsumoto summarized the reactions for which rate enhancement is expected at high pressure.[86]

1. Reactions in which the molecularity number (number of molecules) decreases when starting materials are converted to products: cycloadditions, condensations.
2. Reactions that proceed via cyclic transition states.
3. Reactions that take place through dipolar transition states.
4. Reactions with steric hindrance.

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[84] For example, see Clark, J.H. *Green Chem.* ***1999***, *1*, 1; Cave, G.W.V.; Raston, C.L.; Scott, J.L. *Chem. Commun.* ***2001***, 2159.

[85] Jenner, G. *Tetrahedron* ***2002***, *58*, 5185; Matsumoto, K.; Morris, A.R. *Organic Synthesis at High Pressure*, Wiley, New York, ***1991***.

[86] Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1; Matsumoto, K.; Sera, A. *Synthesis* ***1985***, 999.

[87] See le Noble, W.J. *Progr. Phys. Org. Chem.* ***1967***, *5*, 207; Isaacs, N.S. *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, ***1981***; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978***, *78*, 407.

Many high-pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, and this influences the viscosity of the medium (the viscosity of liquids increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important, leading to another influence of high pressure on reactivity.[86,88] In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place. The temperature is lowered and the pressure is reduced to isolate the products.

WATER AND OTHER NONORGANIC SOLVENTS

Chemical reactions of organic substrates usually employs an organic solvent, such as a hydrocarbon, ether, dichloromethane, and so on. With the exception of small molecular weight molecules with polar functional groups and polyfunctional molecules or salts, organic chemicals have poor solubility in water. The first indication that water accelerated a reaction was in a patent by Hopff and Rautenstrauch in 1939,[89] who reported that yields in the Diels–Alder reaction (**15-60**) were enhanced in aqueous detergent solutions. In an early study, Berson showed a clear relationship between the endo/exo product ratio and solvent polarity, in the Diels–Alder reaction of cyclopentadiene and acrylates.[90] Breslow showed there was a hydrophobic acceleration for an intermolecular Diels–Alder reaction in which cyclopentadiene reacted with methyl vinyl ketone.[91] Clearly, there is an accelerating effect on some chemical reactions when done in water that is useful in organic chemistry.[92]

When nonpolar compounds are suspended in water their relative insolubility causes them to associate, diminishing the water–hydrocarbon interfacial area (a hydrophobic effect). This association is greater in water than in methanol and brings the reactive partners into close proximity, increasing the rate of reaction. Any additive that increases the hydrophobic effect will increase the rate.[91]

Carbon dioxide can be used as a reaction solvent when pressurized (supercritical carbon dioxide, $scCO_2$). Carbon dioxide is nontoxic, inexpensive, abundant, and easily recycled. These properties have made it attractive as an extraction solvent.[93] The low critical temperature of CO_2 (T_c) 31.1 °C ensures that $scCO_2$ is a safe solvent for many applications.[94] There are solubility issues that suggest $scCO_2$ is a rather polar solvent.[95] For example, many systems with hydrocarbon chains are

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[89] Hopff, H.; Rautenstrauch, C.W. *U.S. Patent* 2,262,002, ***1939*** [*Chem. Abstr. 36*: 10469, ***1942***].

[90] Berson, J.A.; Hamlet, Z.; Mueller, W.A. *J. Am. Chem. Soc.* ***1962***, *84*, 297.

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[92] Engberts, J.B.F.N.; Blandamer, M.J. *Chem. Commun.* ***2001***, 1701; Lindström, U.M. *Chem. Rev.* ***2002***, *102*, 2751; Ribe, S.; Wipf, P. *Chem. Commun.* ***2001***, 299.

[93] See Raynie, D.E. *Anal. Chem.* ***2004***, *76*, 4659.

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not very soluble in CO_2.[96] Water/carbon dioxide emulsions have also been employed.[97]

The use of supercritical carbon dioxide ($ScCO_2$) has been explored in many reactions,[98] including catalysis.[99] Some applications of this technique include the electrochemical synthesis of conducting polymers[100] and highly cross-linked polymers[101] in $scCO_2$, the synthesis of octyl palmitate,[102] of carbonated fatty methyl esters,[103] and of methyl carbamates.[104] A carbonylation reaction was done is $ScCO_2$ in the course of a synthesis of trisubstituted cyclopentanes and cyclohexanes as key components of substance P antagonists.[105] A continuous flow acid catalyzed dehydration of alcohols was accomplished in $ScCO_2$.[106] Supercritical fluids are playing an increasingly important role in synthetic organic chemistry.[107]

Other supercritical fluids can be used for chemical reactions, such as supercritical ammonia in the synthesis of labeled guanidines.[108]

IONIC SOLVENTS

Environmentally friendly solvents, such as ionic liquids, is of great interest. It was discovered that some molecules form ionic liquids that are suitable as a medium for chemical reactions.[109] An ionic liquid is a salt in which the ions are poorly coordinated, usually leading to their being liquid $<100°C$ and sometimes at room temperature. In such ionic species, there is usually at least one ion with a delocalized charge whereas the other component is usually organic. This combination inhibits the formation of a stable crystal lattice. Both methylimidazolium and pyridinium ions form the basis of common ionic liquids that have been used in organic chemistry. One of the most common ionic solvents is 1-butyl-3-methylimidazolium as the hexafluorophosopahte, **10**

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[107] Oakes, R.S.; Clifford, A.A.; Rayner, C.M. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 917; Prajapati, D.; Gohain, M. *Tetrahedron* ***2004***, *60*, 815.

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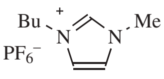
(Bmim PF_6).[110] Hydrogenbutylimidazolium tetrafluoroborate (HBuIm, **11**) and 1,3-dibutylimidazolium, tetrafluoroborate (DiBuIm, **12**), for example,[111] have been reported to facilitate Diels–Alder reactions (**15-60**).[112] Pyridinium based ionic liquids, such as ethylpyridinium tetrafluoroborate (**13**), have also been used.[113]



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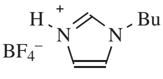

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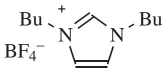

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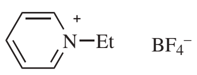

13

Ionic solvents have been used to facilitate the Heck reaction (**13-9**),[114] the oxidation of alcohols with hypervalent iodine reagents (**19-3**),[115] and the catalytic asymmetric dihydroxylation of olefins (**15-48**) using a recoverable and reusable osmium/ligand.[116] Reactions in ionic liquids is a rapidly growing area of organic chemistry, including microwave reactions (see p. 354) in ionic solvents.[117] The development and use of ionic solvents is a growth area of organic chemistry.[118]

SOLVENTLESS REACTIONS

In some cases, it should be possible to accomplish a chemical transformation without the use of a solvent. Dry media reaction under microwaves is an important area of study (see p. 352).[119] There are several advantages of solventless reactions: (*1*) the possibility of direct formation of high purity compounds, (*2*) the possibility of sequential reactions, (*3*) fast kinetics, (*4*) lower energy usage, (*5*) minimal need for preformed salts and metal–metalloid complexes, (*6*) simplicity and low equipment cost, and (*7*) the possibility of avoiding functional group protection–deprotection.[120] Potential difficulties include the possibility of hot spots and runaway reactions, and difficulties in handling solid or highly viscous materials.[121] An example of this approach is the aldol condensation, where a single aldol product was obtained in high yield.[122] 3-Carboxylcoumarins have been produced via a solventless aldol.[120]

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[111] For discussion of HBuIM and DiBuIm, see Harlow, K.J.; Hill, A.F.; Welton, T. *Synthesis* ***1996***, 697; Holbrey, J.D.; Seddon, K.R. *J. Chem. Soc., Dalton Trans.* ***1999***, 2133; Larsen, A.S.; Holbrey, J.D.; Tham, F.S.; Reed, C.A. *J. Am. Chem. Soc.* ***2000***, *122*, 7264.

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