

Either UV-VIS or IR spectroscopy can be combined with the technique of *matrix isolation* to detect and identify highly unstable intermediates. In this method, the intermediate is trapped in a solid inert matrix, usually one of the inert gases, at very low temperatures. Since each molecule is surrounded by inert gas atoms, there is no possibility for intermolecular reactions and the rates of intramolecular reactions are slowed by the low temperature. Matrix isolation is a very useful method for looking for intermediates in photochemical reactions. The method can also be used for gas phase reactions that can be conducted in such a way that the intermediates can be rapidly condensed into the matrix.

Nuclear magnetic resonance (NMR) is very widely used for detection of intermediates in organic reactions. Proton magnetic resonance is most useful because ^1H provides the greatest sensitivity of detection among the nuclei of interest in organic chemistry. Fluorine-19 and phosphorus-31 are other elements that provide high sensitivity. Carbon-13, oxygen-17, and nitrogen-15 provide relatively lower sensitivity, but isotopic enrichment is possible. Initially, NMR suffered from very low sensitivity relative to other spectroscopic methods. However, the development of high-field instruments and the use of Fourier transform methods have greatly increased sensitivity so that NMR can now be used to detect many reaction intermediates.

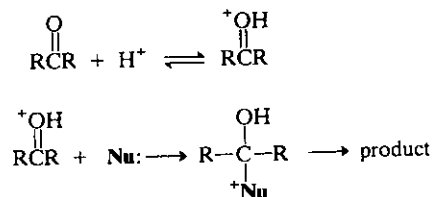
Free radicals and other intermediates with unpaired electrons can be detected in extremely low concentration by electron paramagnetic resonance (EPR). This technique measures the energy absorbed to reorient an electron's spin in a magnetic field. It provides structural information on the basis of splitting of the signal by adjacent nuclei, much as in NMR interpretation. EPR is not only extremely sensitive, but also very specific. Diamagnetic molecules present in solution give no signals, and the possibility for interference is therefore greatly decreased. The method can only be applied to reactions involving paramagnetic intermediates.

All other spectroscopic methods are equally applicable, in principle, to the detection of reaction intermediates so long as the method provides sufficient structural information to assist in the identification of the transient species. In the use of all methods, including those discussed above, it must be remembered that simple detection does not prove the species is an intermediate. It also must be shown that the species is converted to product. In favorable cases, this may be done by isolation or trapping experiments. More often, it may be necessary to determine the kinetic behavior of the appearance and disappearance of the intermediate and demonstrate that it is consistent with the species being an intermediate.

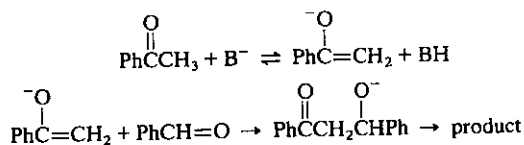
4.8. Catalysis by Acids and Bases

A detailed understanding of a reaction mechanism requires knowledge of the role catalysts play in the reaction. Catalysts cannot affect the position of equilibrium of a reaction. They function by increasing the rate of one or more steps in a reaction mechanism by providing a reaction path having a lower activation energy. The most

general family of catalytic processes are those that involve transfer of a proton. Many reactions involving neutral reactants are strongly catalyzed by proton donors (Brønsted acids) or proton acceptors (Brønsted bases). Catalysis occurs when the conjugate base or conjugate acid of the substrate is a more reactive molecule than the neutral species. For example, reactions involving nucleophilic attack at carbonyl groups are often accelerated by acids. This type of catalysis occurs because the conjugate acid of the carbonyl compound is much more electrophilic than the neutral molecule.



Many important organic reactions involve nucleophilic carbon species (carbanions). The properties of carbanions will be discussed in detail in Chapter 7 and in Part B, Chapters 1 and 2. Most C—H bonds are very weakly acidic and have no tendency to ionize spontaneously to form carbanions. Reactions that involve carbanion intermediates are therefore usually carried out by reaction of the neutral organic molecule and the electrophile in the presence of a base that can generate the more reactive carbanion intermediate. Base-catalyzed condensation reactions of carbonyl compounds provide many examples of this type of reaction. The reaction between acetophenone and benzaldehyde which was considered in Section 4.2, for example, requires a basic catalyst to proceed, and the kinetics of the reaction show that the rate is proportional to the catalyst concentration. This is because the neutral acetophenone molecule is not nucleophilic and does not react with benzaldehyde. The enolate (carbanion) formed by deprotonation is much more nucleophilic.



The role that acid and base catalysts play can be quantitatively studied by kinetic techniques. It is possible to recognize several distinct types of catalysis by acids and bases. The term *specific acid catalysis* is used when the reaction rate is dependent on the equilibrium for protonation of the reactant. This type of catalysis is independent of the concentration and specific structure of the various proton donors present in solution. Specific acid catalysis is governed by the *hydrogen ion concentration* (pH) of the solution. For example, for a series of reactions in an aqueous buffer system, the rate of the reaction would be a function of the pH, but not of the concentration or identity of the acidic and basic components of the buffer. The kinetic expression for any such reaction will include a term for hydrogen ion concentration, $[\text{H}^+]$. When the nature and concentration of proton donors present

in solution affect the reaction rate, the term used is *general acid catalysis*. The kinetic expression for such a reaction will include terms for each of the potential proton donors that act as catalysts. The terms *specific base catalysis* and *general base catalysis* apply in the same way to base-catalyzed reactions.

Specific acid catalysis:

$$\text{rate} = k[\text{H}^+][\text{X}][\text{Y}], \quad \text{where } [\text{X}][\text{Y}] = \text{concentration of the reactants}$$

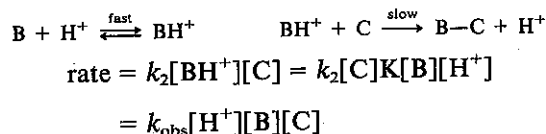
General acid catalysis:

$$\text{rate} = k_1[\text{H}^+][\text{X}][\text{Y}] + k_2[\text{HA}^1][\text{X}][\text{Y}] + k_3[\text{HA}^2][\text{X}][\text{Y}],$$

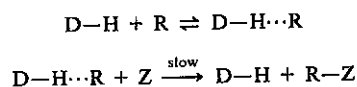
where $\text{HA}^1, \text{HA}^2 \dots$ are all kinetically significant proton donors

The experimental detection of general acid catalysis is done by rate measurements at constant pH but differing buffer concentration. Since under these circumstances $[\text{H}^+]$ is constant but the weak acid component(s) of the buffer (HA^1, HA^2 , etc.) changes, the observation of a change in rate is evidence of general acid catalysis. If the rate remains constant, the reaction exhibits specific acid catalysis. Similarly, general base-catalyzed reactions will show a dependence of the rate on the concentration and identity of the basic constituents of the buffer system.

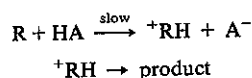
Specific acid catalysis is observed when a reaction proceeds only through a protonated intermediate which is in equilibrium with its conjugate base. Since the position of this equilibrium is a function of the concentration of solvated protons, only a single acid-dependent term appears in the kinetic expression. For example, in a two-step reaction involving rate-determining reaction of one reagent with the conjugate acid of a second, the kinetic expression will be as follows:



Several situations can lead to the observation of general acid catalysis. General acid catalysis can occur as a result of hydrogen bonding between the reactant R and a proton donor D—H to form a reactive complex {D—H...R} which then reacts with a substance Z:

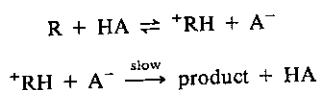


Under these circumstances, a distinct contribution to the overall rate will be seen for each potential hydrogen bond donor D—H. General acid catalysis is also observed when a rate-determining proton transfer occurs from acids other than the solvated proton:



Each acid HA^1 , HA^2 , etc., will then make a contribution to the overall rate of the reaction.

A kinetic expression which is equivalent to that for general acid catalysis also occurs if a prior equilibrium between reactant and the acids is followed by rate-controlling proton transfer. Each individual conjugate base will appear in the overall rate expression:



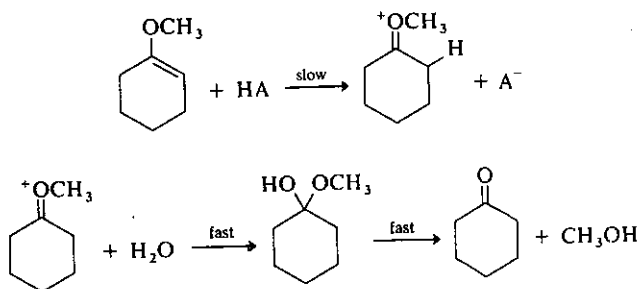
Notice that specific acid catalysis describes a situation where the reactant is in equilibrium with regard to proton transfer, and proton transfer is not rate-determining. On the other hand, each case that leads to general acid catalysis involves proton transfer in the rate-determining step. Because of these differences, the study of rates as a function of pH and buffer concentrations can permit conclusions about the nature of proton transfer processes and their relationship to the rate-determining step in a reaction.

As might be expected intuitively, there is a relationship between the effectiveness of general acid catalysts and the acidity of a proton donor as measured by its acid dissociation constant. This relationship is expressed by the following equation, which is known as the *Brønsted catalysis law*:

$$\log k_{\text{cat}} = \alpha \log K_a + b \quad (4.19)$$

An analogous equation holds for catalysis by bases. This equation requires that the free energies of activation for the catalytic step for a series of acids be directly proportional to the free energies of dissociation for the same series of acids. The proportionality constant σ is an indication of the sensitivity of the catalytic step to structural changes relative to the effect of the same structural changes on acid dissociation. It is often found that a single proportionality constant α is restricted to only structurally related types of acids and that α values of different magnitude are revealed by each type.

Figure 4.10 is plot of the Brønsted relationship for hydrolysis of an enol ether. The plot shows that the effectiveness of the various carboxylic acids as catalysts is related to their dissociation constants. In this particular case, the constant α is 0.79⁴⁰:



40. A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, *J. Am. Chem. Soc.* 93, 413 (1971).

Since acid, transi degree of thi T solver versus on the strong exten involv becau if pro H_2O consi

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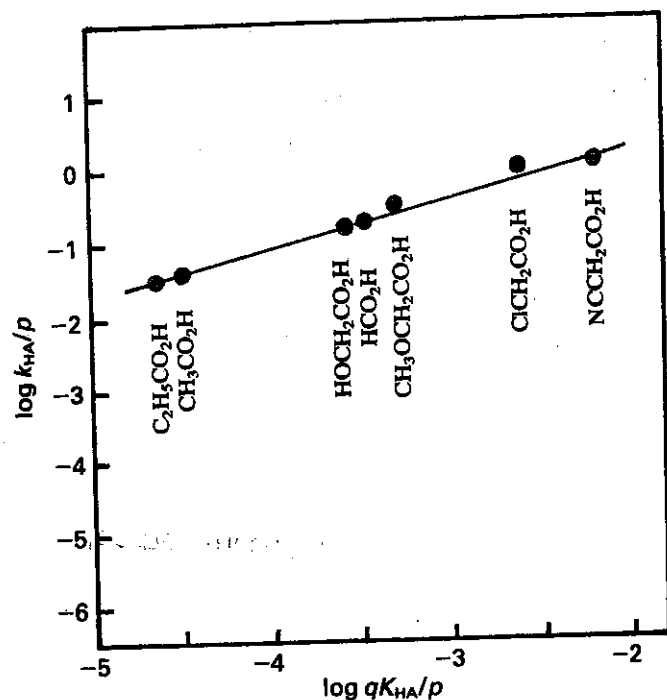


Fig. 4.10. Brønsted relation for the hydrolysis of methyl cyclohexenyl ether. (Adapted from Ref. 40 by permission of the American Chemical Society.)

Since α relates the sensitivity of the proton transfer to that of dissociation of the acid, it is frequently assumed that the value of α can be used as an indicator of transition state structure. The closer α approaches unity, the greater would be the degree of proton transfer in the transition state. There are limits to the generality of this interpretation, however.⁴¹

The details of proton transfer processes can also be probed by examination of *solvent isotope effects*, for example, by comparing the rates of a reaction in H_2O versus D_2O . The solvent isotope effect can be either normal or inverse, depending on the nature of the proton transfer process in the reaction mechanism. D_3O^+ is a stronger acid than H_3O^+ . As a result, reactants in D_2O solution are somewhat more extensively protonated than in H_2O at identical acid concentration. A reaction that involves a rapid equilibrium protonation will proceed faster in D_2O than in H_2O , because of the higher concentration of the protonated reactant. On the other hand, if proton transfer is part of the rate-determining step, the reaction will be faster in H_2O than in D_2O because of the normal primary kinetic isotope effect of the type considered in Section 4.5.

41. A. J. Kresge, *J. Am. Chem. Soc.* **92**, 3210 (1970); R. A. Marcus, *J. Am. Chem. Soc.* **91**, 7224 (1969); F. G. Bordwell and W. J. Boyle, Jr., *J. Am. Chem. Soc.* **94**, 3907 (1972); D. A. Jencks and W. P. Jencks, *J. Am. Chem. Soc.* **99**, 7948 (1977); A. Pross, *J. Org. Chem.* **49**, 1811 (1984).

The interpretation of solvent isotope effects can be complicated by the large number of secondary isotope effects that can conceivably operate when it is the solvent molecule that is the site of isotopic substitution. The quantitative evaluation of solvent isotope effects is a very difficult problem. The relationship between the magnitude of the solvent isotope effect and the occurrence of equilibrium protonation as opposed to rate-limiting proton transfer is sufficiently general to be of value in mechanistic studies. As with nearly all mechanistic criteria, however, there are circumstances that permit exceptions, so corroborating evidence from other studies is always desirable.

Many organic reactions involve acid concentrations considerably higher than can be accurately measured on the pH scale, which applies to relatively dilute aqueous solutions. It is not difficult to prepare solutions in which the formal proton concentration is 10 *M* or more, but these formal concentrations are not a suitable measure of the *activity* of protons in such solutions. For this reason, it has been necessary to develop *acidity functions* to measure the proton-donating strength of concentrated acidic solutions. The activity of the hydrogen ion (solvated proton) can be related to the extent of protonation of a series of bases by the equilibrium expression for the protonation reaction:

$$B + H^+ \rightleftharpoons {}^+BH$$

$$K = \frac{(a_{{}^+BH})}{(a_{H^+})(a_B)} = \frac{[{}^+BH]\gamma_{{}^+BH}}{a_{H^+} + [B]\gamma_B}$$

where γ is the activity coefficient for the base and its conjugate acid. A common measure of acidity is referred to as h_0 and is defined by measuring the extent of protonation of a series of bases for which K has been measured. The relative concentration of the base and its conjugate acid then defines h_0 for any particular acidic solution.

$$h_0 = \frac{[{}^+BH]\gamma_{{}^+BH}}{K[B]\gamma_B}$$

The quantity H_0 , defined as $-\log h_0$, is commonly tabulated, and it corresponds to the "pH" of very concentrated acidic solutions.

The problem of determining K independently of measurement of H_0 is the principal issue to be faced in establishing the H_0 scale for a series of acidic solutions. What is done is to measure K for some base in aqueous solution where $H_0 \approx \text{pH}$. This base can then be used to find the H_0 of a somewhat more acidic solution. The K of a second, somewhat weaker base is then determined in the more acidic solution. This second base can then be used to extend H_0 into a still more acidic solution. The process is continued by using a series of bases to establish H_0 for successively more acidic solution. The H_0 is thereby referenced to the original aqueous measurement.⁴² The assumption involved in this procedure is that the ratio of the activity

42. For reviews and discussion of acidity functions, see E. M. Arnett, *Prog. Phys. Org. Chem.* **1**, 223 (1963); C. H. Rochester, *Acidity Functions*, Academic Press, New York, 1970; R. A. Cox and K. Yates, *Can. J. Chem.* **61**, 225 (1983); C. D. Johnson and B. Stratton, *J. Org. Chem.* **51**, 4100 (1986).

coefficients for the series of bases and the series of cations does not change from solvent to solvent, that is,

$$\frac{\gamma_{B_1H}^+}{\gamma_{B_1}} = \frac{\gamma_{B_2H}^+}{\gamma_{B_2}} = \frac{\gamma_{B_3H}^+}{\gamma_{B_3}} \dots \text{etc.}$$

Not unexpectedly, this procedure reveals some dependence on the particular type of base used, so no absolute H_0 scale can be established. Nevertheless, this technique provides a very useful measure of the relative hydrogen ion activity of concentrated acid solutions that can be used in the study of reactions that proceed only at high acid concentration. Table 4.6 gives H_0 values for some water-sulfuric acid mixtures.

4.9. Lewis Acid Catalysis

Lewis acids are defined as molecules which act as electron pair acceptors. The proton is an important special case, but many other species can play an important role in the catalysis of organic reactions. The most important in organic reactions are metal cations and covalent compounds of metals. Metal cations which play prominent roles as catalysts include the alkali metal monocations Li^+ , Na^+ , K^+ , Cs^+ , and Rb^+ , the divalent ions Mg^{2+} , Ca^{2+} , and many of the transition metal cations. The most commonly employed of the covalent compounds include boron trifluoride, aluminum trichloride, titanium tetrachloride, and stannic tetrachloride. Various other derivatives of boron, aluminum, and titanium also are employed as Lewis acid catalysts.

The catalytic activity of metal ions originates in the formation of a donor-acceptor complex between the cation and the reactant, which must act as a Lewis base. The result of the complexation is that the donor atom becomes effectively more electronegative. All functional groups that have unshared electron pairs are

Table 4.6. H_0 as a Function of Composition of Aqueous Sulfuric Acid^a

%H ₂ SO ₄	H_0	%H ₂ SO ₄	H_0
5	0.24	55	-3.91
10	-0.31	60	-4.46
15	-0.66	65	-5.04
20	-1.01	70	-5.80
25	-1.37	75	-6.56
30	-1.72	80	-7.34
35	-2.06	85	-8.14
40	-2.41	90	-8.92
45	-2.85	95	-9.85
50	-3.38	98	-10.41

a. From M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.* **85**, 878 (1963).