MECHANISM
AND THEORY
IN
ORGANIC CHEMISTRY

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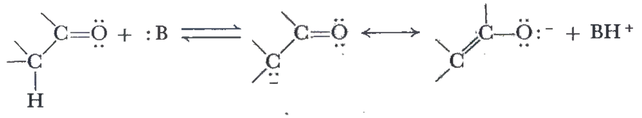
Chapter 8

REACTIONS OF CARBONYL COMPOUNDS

Carbonyl compounds comprise a large and important class of organic substances, and the chemistry of this functional group is essential to the understanding of many chemical and biochemical processes.[1] In this chapter we use a few fundamental ideas of mechanism to correlate reactions of various carbonyl functional groups. We shall touch briefly on the closely related chemistry of carbon–nitrogen double bonds.

Carbonyl reactions may be understood in terms of two basic processes: addition of a nucleophile to the carbonyl carbon (Equation 8.1) and removal of a proton from the carbon adjacent to the carbonyl group (Equation 8.2). In the first process the carbonyl molecule is acting as a Lewis acid, and in the second


(8.1)


(8.2)

(which is, of course, possible only if the molecule bears an α-hydrogen) as a Brønsted acid. Both depend on the electron deficiency of the carbonyl carbon, which is in turn caused by the electronegativity of the oxygen and its ability to accept a negative charge. The second reaction is readily reversible, and the first under most circumstances is also. Coordination of the carbonyl oxygen with a proton or some other Lewis acid will make the oxygen more electrophilic and may be expected to facilitate both addition of a nucleophile to the carbonyl carbon and removal of a proton from the α position. Catalysis by acids and bases is thus a central theme of carbonyl reactions.

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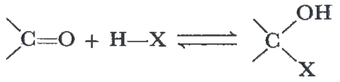
[1] Reviews of various aspects of carbonyl chemistry may be found in the following sources: (a) W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw–Hill, New York, 1969; (b) W. P. Jencks, *Prog. Phys. Org. Chem.*, **2,** 63 (1964); (c) R. P. Bell, *Advan. Phys. Org. Chem.*, **4,** 1 (1966); (d) S. Patai, Ed., *The Chemistry of the Carbonyl Group*, Vol. 1, and J. Zabicky, Ed., *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley–Interscience, London, 1966 and 1970; (e) S. Patai, Ed., *The Chemistry of Acyl Halides*, Wiley–Interscience, London, 1972.

8.1 HYDRATION AND ACID–BASE CATALYSIS

We consider first the simple addition of a nucleophile to a carbonyl carbon, preceded, accompanied, or followed by addition of a proton to the oxygen, and the reverse. The overall process (Equation 8.3) amounts to addition of H—X to C═O. The reaction differs from the additions to C═C discussed in Chapter 7 in two important respects. First, the nucleophile always becomes bonded to the


(8.3)

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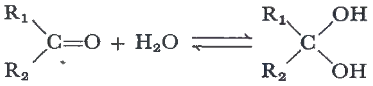
carbon and the proton to the oxygen, so there is no ambiguity concerning direction of addition; and second, the C═O group is much more susceptible to attack by a nucleophile than is C═C.

Hydration

Water adds to the carbonyl group of aldehydes and ketones to yield hydrates (Equation 8.4). For ketones and aryl aldehydes, equilibrium constants of the


(8.4)

R_1, R_2 = H, alkyl, aryl

reaction as written are much less than unity, but aliphatic aldehydes are appreciably hydrated in water solution. The equilibrium constant is larger for the lower aldehydes and is largest for formaldehyde. Some representative values are given in Table 8.1. Bulky groups and groups that donate electron density to the electron-deficient carbonyl carbon stabilize the carbonyl form, whereas substituting electron-withdrawing groups, or incorporating the carbonyl carbon in a strained ring,[2] favors the hydrate. Equilibrium constants correlate with Taft inductive and steric parameters.[3]

Mechanistic questions in the hydration–dehydration equilibrium center around the acid–base relationships and the precise sequence of events in the addition or elimination of the water molecule. Investigations have relied primarily on kinetics of aldehyde hydration to elucidate the mechanistic details;

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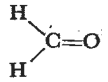
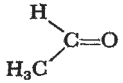
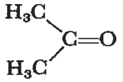
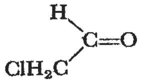
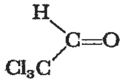
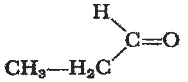
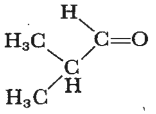
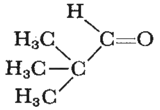
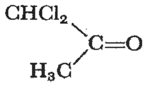
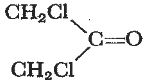
[2] (a) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Amer. Chem. Soc.*, **73,** 212 (1951); (b) J. F. Pazos, J. G. Pacifici, G. O. Pierson, D. R. Sclove, and F. D. Greene, *J. Org. Chem.*, **39,** 1990 (1974); see also (c) N. J. Turro and W. B. Hammond, *J. Amer. Chem. Soc.*, **88,** 3672 (1966).

[3] (a) Y. Ogata and A. Kawasaki, in *The Chemistry of the Carbonyl Group*, Zabicky, Ed., Vol. 2, p. 1; (b) P. Greenzaid, Z. Luz, and D. Samuel, *J. Amer. Chem. Soc.*, **89,** 749 (1967).

Table 8.1 APPROXIMATE EQUILIBRIUM CONSTANTS AT 25°C FOR THE REACTION
$R_1R_2C{=}O + H_2O \rightleftharpoons R_1R_2C(OH)_2$

Carbonyl Compound	$K[H_2O] = \frac{[R_1R_2C(OH)_2]}{[R_1R_2C{=}O]}$ [a]
	2×10^3
	1.3
	2×10^{-3}
	37
	2.8×10^4
	0.71
	0.44^b
	0.24^b
	2.9
	10

[a] Except as noted, values are from R. P. Bell, *Advan. Phys. Org. Chem.*, **4,** 1 (1966).
[b] P. Greenzaid, Z. Luz, and D. Samuel, *J. Amer. Chem. Soc.*, **89,** 749 (1967).

rates of reaction in both directions have been measured by spectroscopic methods,[4] isotope exchange experiments,[5] heat of reaction,[6] volume change measurements,[7] and by scavenging liberated aldehyde.[8] The reaction is subject to general acid and general base catalysis.[9]

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[4] (a) P. Greenzaid, Z. Luz, and D. Samuel, *J. Amer. Chem. Soc.*, **89,** 756 (1967); (b) M.-L. Ahrens and H. Strehlow, *Disc. Faraday Soc.*, **39,** 112 (1965); (c) R. P. Bell and M. B. Jensen, *Proc. Roy. Soc.*, **A261,** 38 (1961).
[5] M. Cohn and H. C. Urey, *J. Amer. Chem. Soc.*, **60,** 679 (1938).
[6] R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52,** 1093 (1956).

General Acid and Base Catalysis

We have already encountered general catalysis in Section 7.1 (p. 340). Because it is so important to the understanding of carbonyl reactions, we shall consider it here in more detail. The discussion will be restricted to aqueous solutions, because these have been the most thoroughly studied.

Suppose that acid catalyzes a reaction by forming the conjugate acid of the substrate in a rapid equilibrium preceding a slower step, as indicated in Scheme 1.

SCHEME 1

$$S + HA \underset{}{\overset{\text{fast}}{\rightleftharpoons}} SH^+ + A^-$$

$$SH^+ \xrightarrow[k]{\text{slow}} \text{products}$$

The reaction rate is given by Equation 8.5. Concentration $[SH^+]$ is in turn determined by the preliminary equilibrium, for which we may write the equilibrium constant K (Equation 8.6). But concentrations [HA] and $[A^-]$ are themselves related to $[H_3O^+]$ through the K_a for the acid HA (Equation 8.7). Combination of Equations 8.6 and 8.7 shows that under these circumstances the concentration of reactive species, SH^+, is actually determined by the H_3O^+ concentration and the K_a of SH^+ (Equations 8.8 and 8.9). The reaction rate (Equation 8.10) depends on the H_3O^+ concentration, and the reaction is said to be subject to *specific acid catalysis*. An entirely analogous argument can be made for a base-catalyzed reaction with a preliminary equilibrium to form the conjugate base of the substrate. Such a reaction shows *specific base catalysis*. Note that the mechanism of Scheme 1, which gives only specific catalysis, does not involve any proton transfer in the rate-determining step.

$$\text{rate} = k[SH^+] \tag{8.5}$$

$$K = \frac{[SH^+][A^-]}{[S][HA]} \tag{8.6}$$

$$K_{a_{HA}} = \frac{[H_3O^+][A^-]}{[HA]} \tag{8.7}$$

$$\frac{K}{K_{a_{HA}}} = \frac{[SH^+][A^-]}{[S][HA]}\,\frac{[HA]}{[A^-][H_3O^+]} \tag{8.8}$$

$$\frac{K}{K_{a_{HA}}} = \frac{[SH^+]}{[S][H_3O^+]} = \frac{1}{K_{a_{SH^+}}} \tag{8.9}$$

$$\text{rate} = \frac{k}{K_{a_{SH^+}}}[S][H_3O^+] \tag{8.10}$$

Another possibility is that the proton transfer itself constitutes the rate-determining step, or that the rate-determining step consists of proton transfer

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[7] R. P. Bell and B. de B. Darwent, *Trans. Faraday Soc.*, **46,** 34 (1950).
[8] R. P. Bell and P. G. Evans, *Proc. Roy. Soc.*, **A291,** 297 (1966).
[9] Discussions of the acid–base catalysis may be found in the reviews cited in note 1.

occurring simultaneously with some other process. An example is the deprotonation of carbon acids, which we discussed in Section 3.3 (p. 141), when we considered the Brønsted catalysis law relating the effectiveness of the catalyst to its equilibrium acidity. Under these circumstances each individual acid (or base) present in the system can act as a proton donor (or acceptor) in the rate-determining step, and the rate of this step then depends on each of these acids (bases) individually, as indicated in Equation 8.11 for an acid-catalyzed process. A reaction that follows Equation 8.11 is said to be subject to *general acid catalysis*; the analogous situation with base catalysis is *general base catalysis*.

$$\text{rate} = k_0 + k_{\mathrm{H}^+}[\mathrm{H_3O^+}] + k_1[\mathrm{HA_1}] + k_2[\mathrm{HA_2}] + \cdots \tag{8.11}$$

The Brønsted catalysis law states that the individual catalytic constants, k_n, should be related to the equilibrium acidities by Equation 8.12, or, for a base-catalyzed process, by Equation 8.13. (See Section 3.3, p. 141, for further discussion of these relations.) The Brønsted slope α (β for base catalysis) is a measure of the sensitivity of the reaction to the acid strengths of the various catalysts.

$$\text{Acid catalysis:} \quad \log k_n = \alpha \log K_{a_n} + \log C \quad \text{or} \quad k_n = CK_{a_n}^{\alpha} \tag{8.12}$$

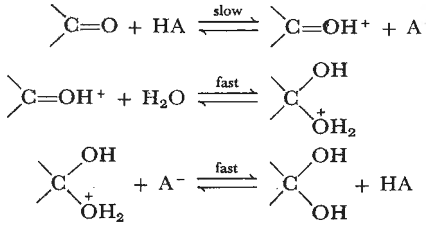
$$\text{Base catalysis:} \quad \log k_n = -\beta \log K_{a_{\mathrm{BH}^+}} + \log C' \quad \text{or} \quad k_n = C'K_{a_{\mathrm{BH}^+}}^{-\beta} \tag{8.13}$$

If for a particular reaction α is near 1.0, most of the catalysis will be by the strongest acid (H_3O^+ in aqueous solution); catalysis by weaker acids will then be difficult or impossible to detect, and the situation will be indistinguishable kinetically from specific catalysis. If α is near zero, all acids will be equally effective, but since the solvent is present in much higher concentration than any other acid, it will be the predominant catalyst and again the catalysis by other acids will be difficult to detect.

The usual means of finding general catalysis is to measure reaction rate with various concentrations of the general acids or bases but a constant concentration of H_3O^+. Since the pH depends only on the ratio of [HA] to [A^-] and not on the absolute concentrations, this requirement may be satisfied by the use of buffers. Catalytic rate constants have been measured for a number of acids and bases in aldehyde hydration–dehydration, notably by Bell and co-workers.[10] For formaldehyde, $\alpha = 0.24$, $\beta = 0.40$; earlier work[11] gave for acetaldehyde $\alpha = 0.54$, $\beta = 0.45$ and for symmetrical dichloroacetone $\alpha = 0.27$, $\beta = 0.50$.

The observation of general catalysis means that proton transfer must be involved in the rate-determining step.[12] Much has been learned about kinetics of proton transfer from fast-reaction techniques developed largely by Eigen and co-workers; absolute rate constants for many proton transfers are known.[13] The rates of simple proton transfers between oxygen atoms or oxygen and nitrogen are extremely fast, and become diffusion-controlled when the equilibrium constant is favorable in the direction in which the proton is being transferred. These observations have generally been considered to rule out a mechanism for carbonyl hydration in which simple proton transfer is the rate-determining step (Scheme 2). Such a process would have to proceed faster than is observed in order to be consistent with Eigen's data. There do, nevertheless, appear to be reactions in which simple proton transfer to or from a highly reactive intermediate is rate-determining, but which are nevertheless slow simply because the concentration of that intermediate is very small.[14]

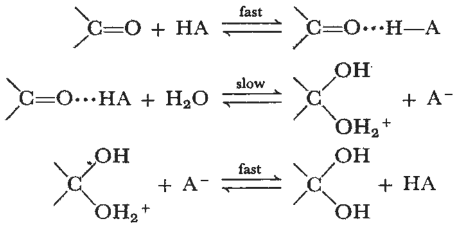
SCHEME 2



Simultaneous Proton Transfer and Attack of Nucleophile

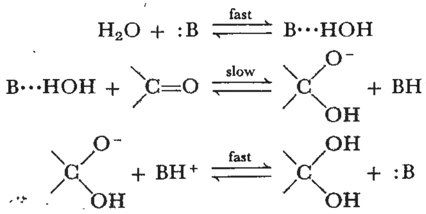
The alternative that appears to offer a consistent explanation for hydration is that proton transfer occurs simultaneously with addition of the nucleophile.

SCHEME 3



The mechanism shown in Scheme 3 envisions an association by hydrogen bonding between the catalyst and the carbonyl compound, followed by rate-determining attack of the nucleophile (H_2O) and simultaneous transfer of the proton. The rate of this step will depend on the nature and concentration of HA, and the mechanism is consistent with general catalysis. It should be noted that the reverse process consists of a specific acid plus a general base catalysis. A possible general base catalysis mechanism is shown in Scheme 4. The reverse is a specific base plus a general acid catalysis.

SCHEME 4



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[10] See note 8, p. 405.

[11] See note 6, p. 404, and note 4(c), p. 404.

[12] It may, of course, happen that no one step is rate-determining. The requirement then is that proton transfer must be part of at least one of the group of steps that together constitute the rate-determining process.

[13] M. Eigen, *Angew. Chem. Int. Ed.*, **3**, 1 (1964).

[14] R. E. Barnett, *Accts. Chem. Res.*, **6**, 41 (1973).

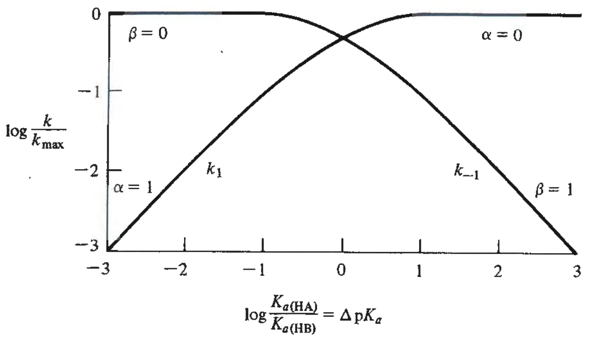

Figure 8.1 Logarithm of the rate of a simple proton transfer of the type

$$HA + B^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A^- + HB$$

as a function of the relative strength of the acids HA and HB. When equilibrium lies toward the right (log $[K_{a(HA)}/K_{a(HB)}]$ positive), k_1 is diffusion-controlled and $\alpha = 0$; when equilibrium lies toward the left (log$[K_{a(HA)}/K_{a(HB)}]$ negative), k_{-1} is diffusion-controlled and $\beta = 0$. From M. Eigen, *Angew. Chem., Int. Ed.*, **3,** 1 (1964). See also J. N. Brønsted and K. Pedersen, *Z. Phys. Chem.*, **108,** 185 (1924). (Angewandte Chemie, *International Edition in English*, Vol. 3 (1964), from the paper by M. Eigen beginning on p. 1. Reproduced by permission of Verlag Chemie, GMBH.)

The mechanism with simultaneous proton transfer and nucleophile attack helps account for another phenomenon observed by Eigen.[15] He found that, for simple proton transfers between oxygen atoms or between oxygen and nitrogen atoms, the proton transfer rate responds as shown in Figure 8.1 to changes in relative acidity of the two acids.[16] In Reaction 8.14, suppose that the structure of acid HA is varied so as to change its strength, but HA is kept substantially

$$HA + B^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A^- + HB \tag{8.14}$$

$$\log k_1 - \log k_{-1} = \log K = \log \frac{K_{a_{HA}}}{K_{a_{HB}}} = \Delta pK_a \tag{8.15}$$

stronger than HB. Then the rate (k_1) of proton transfer from HA to B^- will be diffusion-controlled ($k_1 = k_{max}$) and will not change as HA changes. Interpreted from the point of view of the Brønsted catalysis law, a rate that is independent of acid strength means that $\alpha = 0$ (k_1 curve, right-hand side of Figure 8.1). The reverse reaction in this same region of relative acid strength would be considered a base catalysis by bases A^- of varying strength. Equation 8.15 shows that, with $k_1 = k_{max}$, log k_{-1} will be linearly related, with a slope of unity, to ΔpK_a when the latter is varied by changing A^-. Hence $\beta = 1$, as shown by the k_{-1} curve on the right side of Figure 8.1. The same reasoning, this time with HB as the stronger acid, generates the left side of the figure. Each curve changes slope from unity to zero over a relatively narrow range. These results are in accord with the interpretation based on the Hammond postulate in Section 3.3 (p. 141). Eigen's data suggest that in an acid-catalyzed reaction in which the rate-determining step is a simple proton transfer between oxygens, the α relating rate (k_1) to strength of catalyst ($K_{a_{HA}}$) should be either zero or unity if the catalyst, HA, is a much stronger or a much weaker acid than the protonated substrate, HB. Intermediate values of α should be found when the two are of similar strength.

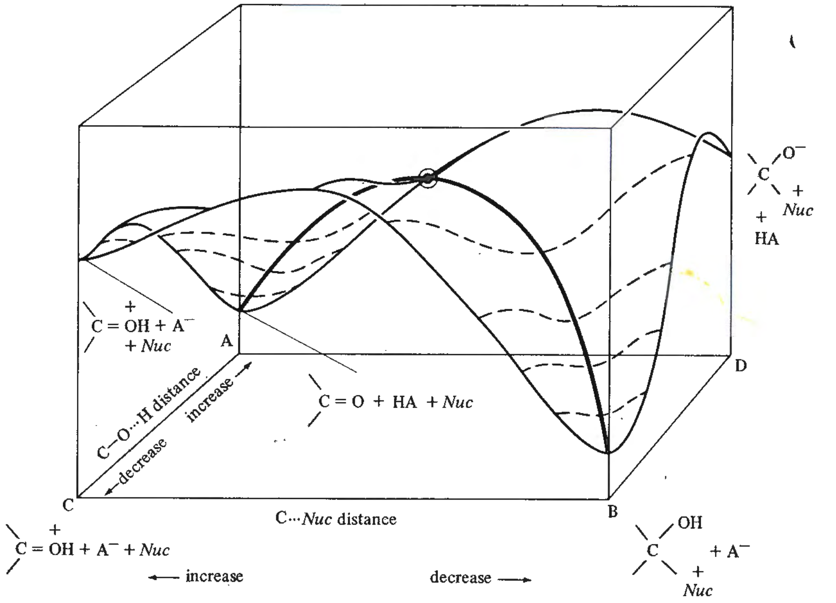

Figure 8.2 Energy surface for addition of nucleophile *Nuc* to a carbonyl with concerted proton transfer from an acid HA. The lowest-energy path is indicated by the heavy line from point A to point B. Points C and D are the high-energy intermediates of the two possible stepwise paths. The circled point is the transition state.

Brønsted anticipated this kind of behavior when he originally proposed the catalysis law,[17] but investigators in intervening years lost sight of the prediction because in many cases, as in carbonyl hydration, α is found to be constant and different from unity over quite a wide range of catalysts. The reason is that in these reactions some other process is occurring simultaneously with proton transfer. Figure 8.2 gives a schematic representation of the energy surface for a concerted addition and proton transfer; Figure 8.3 is the projection of the reaction coordinate in the horizontal plane.[18] In the figures, the reaction begins with carbonyl compound, nucleophile, and acid catalyst (point A) and proceeds directly to point B by simultaneous addition of nucleophile and transfer of proton, thereby avoiding the higher-energy stepwise alternatives through points C and D.

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[15] See note 13, p. 406.

[16] If the acids are of different charge types, the curve is modified somewhat. See note 13.

[17] J. N. Brønsted and K. Pedersen, *Z. Phys. Chem.*, **108,** 185 (1924).

[18] For further discussion of three-dimensional reaction coordinate diagrams for these processes, see Section 5.4, p. 246, and (a) W. P. Jencks, *Chem. Rev.*, **72,** 705 (1972). (b) M. Choi and E. R. Thornton, *J. Amer. Chem. Soc.*, **96,** 1428 (1974), have suggested the possibility of more complex reaction paths with two consecutive transition states not separated by any energy minimum and with reaction coordinates perpendicular to each other on the potential energy surface.

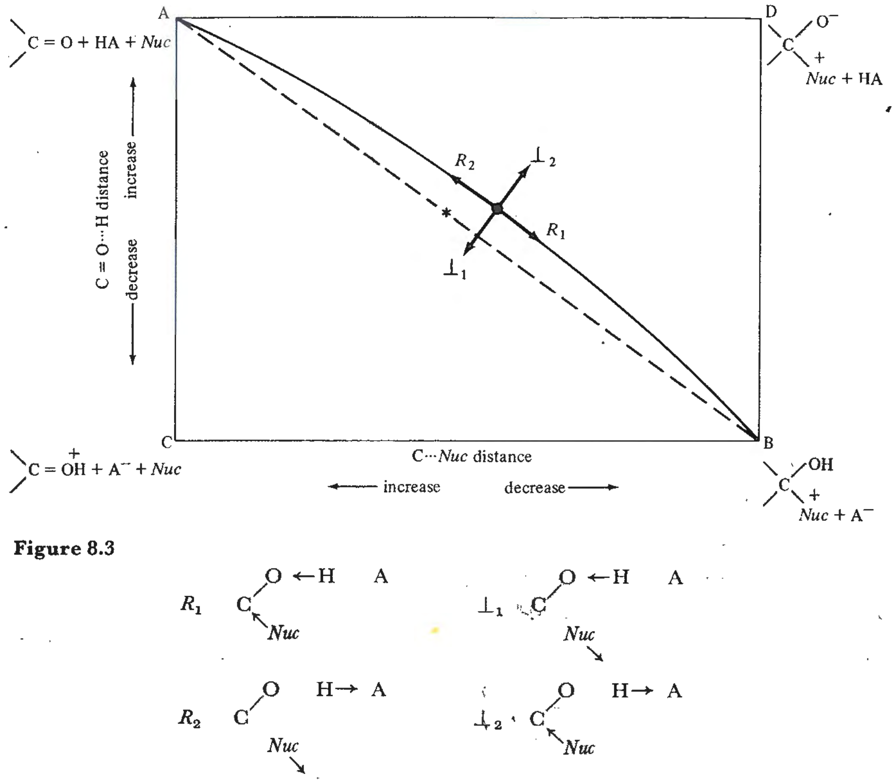


Figure 8.3

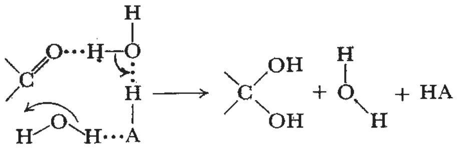
Projection in the horizontal plane of the reaction path shown in Figure 8.2. An increase in the strength of HA will facilitate motions R_1 and $\perp_1$, causing shift of the transition state to $*$ and change of the reaction path from the solid curve to the dashed curve.

In order to relate the Brønsted coefficient α to the reaction coordinate diagrams, we interpret α as a measure of the position of the proton at the transition state, α near zero (HA very strong) indicating an earlier transition state with little proton transfer and α near unity (HA very weak) indicating a late transition state with proton nearly completely transferred. We have already given a partial justification for this interpretation of α in the discussion in Section 3.3; we shall return to this point again later. It is nevertheless important to emphasize here that in a process involving simultaneous proton transfer and nucleophilic addition, α measures only the degree of proton transfer at the transition state (location along the back-to-front coordinate in Figure 8.2 and along the top-to-bottom coordinate in Figure 8.3) and not the degree of bonding of the nucleophile.

As the proton is partly transferred at the transition state in Figure 8.3, α will have a value intermediate between zero and one. We may use the reacting bond rule discussed in Section 2.6 (p. 104) to find the effect of a change in strength of the catalyzing acid HA on the position of the transition state. Recall that reacting bond Rule 1 (equivalent to the Hammond postulate) states that a change in reactants that facilitates motion along the reaction coordinate (motion R_1, Figure 8.3) will move the transition state to an earlier point. Since strengthening acid HA facilitates motion R_1 (transfer of proton from HA to carbonyl oxygen coupled with attack of nucleophile), the transition state will tend to come earlier with respect to this motion; that is, it will be shifted in the direction indicated by the arrow R_2 in Figure 8.3. But proton motion is also involved in the vibration designated by $\perp_1$ and $\perp_2$ in Figure 8.3; reacting bond Rule 2 states that change in structure will shift the transition state in the direction indicated by the change. Here, strengthening acid HA aids motion $\perp_1$.

The composite result of the tendencies for transition state shift in the mutually perpendicular directions R_2 and $\perp_1$ is to move it to the point designated by $*$ in Figure 8.3. The extent of proton transfer is thus not much changed from what it was before, despite the stronger acid HA. Therefore α will be relatively little affected by changes in strength of catalyzing acid and will not pass as quickly through the transition region (near $\Delta pK_a = 0$ in Figure 8.1) as it would have had the proton transfer not been coupled to nucleophile attack.

In some cases of general catalysis it is found that the final rapid proton transfer (for hydration, the last step of Scheme 3 or Scheme 4) occurs at a rate faster than would be possible if the conjugate base (or conjugate acid in a base catalysis) of the catalyst actually moved away from the immediate solvation shell of the substrate to become part of the general solution. Eigen has proposed that this last step may be accomplished simultaneously with the rate-determining step by means of a cyclic transition state that includes one or more extra water molecules, as indicated in the hydration case by Structure 1.[19] When the catalyst is a carboxylic acid, the proton transfer from the catalyst may occur at one of the carboxylate oxygens while the other accepts the proton from the attacking nucleophile.



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(8.16)

The Brønsted α and β as Measures of Transition State Location

We have made use above of the idea that the magnitude of α (or β) measures the extent of proton transfer at the transition state or, equivalently, of the position of the transition state along the proton-transfer reaction coordinate. Figures 8.4 and 8.5 show, respectively, the reaction coordinate diagrams drawn according to the Hammond postulate for Reaction 8.17 in the extreme cases where HX is a

$$HX + Y^- \rightleftharpoons X^- + HY \qquad (8.17)$$

much weaker or a much stronger acid than HY. In the former case (Figure 8.4), $x_\ddagger$ close to unity, small structural changes that alter the free energy of products, G_p°, will cause a similar change in transition state free energy, $G^\ddagger$, whereas changes in reactant free energy, G_r°, will have little effect. This case corresponds

colo
isso
na
Fi

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[19] (a) M. Eigen, *Disc. Faraday Soc.*, 39, 7 (1965); (b) R. P. Bell, J. P. Millington, and J. M. Pink, *Proc. Roy. Soc.*, A303, 1 (1968).

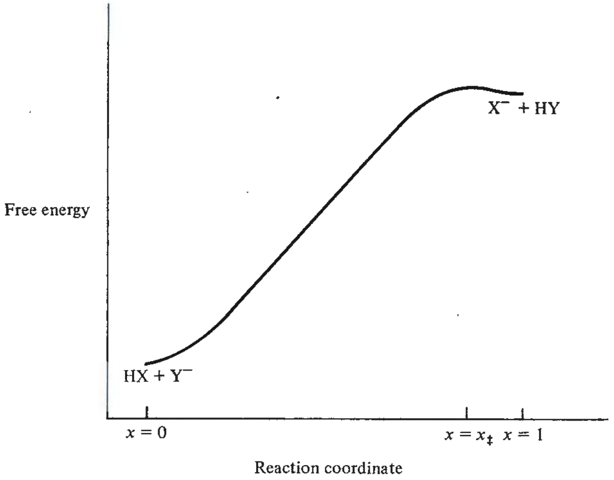

Figure 8.4 Reaction coordinate diagram for the proton transfer $HX + Y^- \rightleftharpoons X^- + HY$, where HX is a weaker acid than HY.

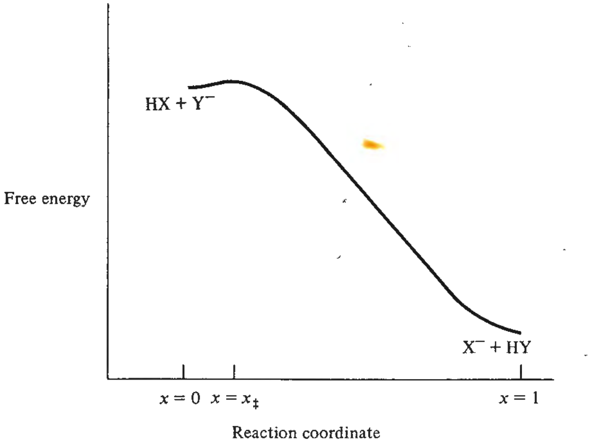

Figure 8.5 Reaction coordinate diagram for the proton transfer $HX + Y^- \rightleftharpoons X^- + HY$, where HX is a stronger acid than HY.

to $\alpha = 1$, $\beta = 0$ in Figure 8.1, that is, reverse reaction diffusion-controlled. Figure 8.5 depicts the opposite extreme, $x_‡$ close to zero, where $G^‡$ depends on G_r° and not G_p°; this case corresponds to forward reaction diffusion-controlled, $\alpha = 0$ and $\beta = 1$ in Figure 8.1. In the intermediate region (center part of Figure 8.1), α varies from 1 to 0 as the transition state moves from being near products (Figure 8.4) to near reactants (Figure 8.5). If we let the symbol δ be an operator designating change in a thermodynamic quantity caused by structural change in the molecules involved,[20] the predictions of the Hammond postulate may be roughly quantified by using α and β as the parameters relating $G^‡$ to G_r° and G_p° as shown in Equation 8.18, where $0 < \alpha < 1$ and $0 < \beta < 1$.[21] If we also assume that $\beta = 1 - \alpha$ (see Figure 8.1) and remember that $\Delta G^‡ = G^‡ - G_r^\circ$ and $\Delta G^\circ = G_p^\circ - G_r^\circ$, we obtain Equation 8.19 by subtracting δG_r° from both sides of

$$\delta G^‡ = \alpha\, \delta G_p^\circ + \beta\, \delta G_r^\circ \tag{8.18}$$

$$\delta G^‡ - \delta G_r^\circ = \alpha\, \delta G_p^\circ + (1 - \alpha)\, \delta G_r^\circ - \delta G_r^\circ \tag{8.19}$$

$$\delta G^‡ - \delta G_r^\circ = \alpha\{\delta G_p^\circ - \delta G_r^\circ\} \tag{8.20}$$

$$\delta \Delta G^‡ = \alpha\, \delta \Delta G^\circ \tag{8.21}$$

Equation 8.18 and find relation 8.21 between activation free energy, $\Delta G^‡$, and standard free energy change, ΔG°. This equation is equivalent to the Brønsted catalysis law as was shown in Section 3.3 (Equations 3.49 and 3.53), and we may conclude that an interpretation of α as a measure of the position of the transition state is consistent with the Hammond postulate.

It should be emphasized again that these arguments apply only to the proton transfer coordinate, and do not give information about the progress of another process that may be concerted with it.[22] Another complication can arise when the proton transfer is to or from a soft center and accompanied by considerable redistribution of charge, as in a carbon acid with an anion-stabilizing group. Bordwell and co-workers have found values of α greater than unity and less than zero for deprotonation and protonation of nitroalkanes; the simple interpretation of this parameter that we have outlined clearly does not apply to such cases.[23] An alternative measure of position of transition state is the deuterium isotope effect; in a simple proton transfer, k_H/k_D should be at a maximum for a transition state in which the proton is midway between the two basic centers.[24] Again, however, the situation is more complex if another process is concerted with proton transfer.

The Mechanistic Ambiguity in General Catalysis

In addition to the problems of interpretation of α and β, certain other difficulties remain. We have assumed that the observation of general acid catalysis implies proton transfer from acid catalyst to substrate in the rate-determining step (Mechanism I, Scheme 5). Mechanism II in Scheme 5 shows that preliminary fast equilibrium yielding the conjugate acid of the substrate followed by a rate-determining step in which a proton is transferred from the protonated substrate to the conjugate base of the catalyst predicts the same dependence on substrate, catalyst, and nucleophile concentrations. Furthermore, the catalysis law (Equations 8.12 and 8.13) shows that when HA is changed, the observed rate constant of Mechanism I, k_1, is proportional to $K_{a_{HA}}^{\alpha}$. In Mechanism II, k_1' is proportional

$\ln k_1 \sim \alpha K_{aHA}$

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[20] J. E. Leffler and E. Grunwald, *Rates and Equilibria of Organic Reactions*, Wiley, New York, 1963, p. 26.

[21] (a) Leffler and Grunwald, *Rates and Equilibria of Organic Reactions*, p. 156; (b) M. Bender, *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley–Interscience, New York, 1971, p. 85.

[22] For a discussion, see G. F. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3982 (1966).

[23] F. G. Bordwell, W. J. Boyle, Jr., and K. C. Yee, *J. Amer. Chem. Soc.*, **92**, 5926 (1970).

[24] (a) R. P. Bell, *Disc. Faraday Soc.*, **39**, 16 (1965); (b) R. A. More O'Ferrall and J. Kouba, *J. Chem. Soc. B*, 985 (1967); (c) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961); see Section 2.7, p. 108.

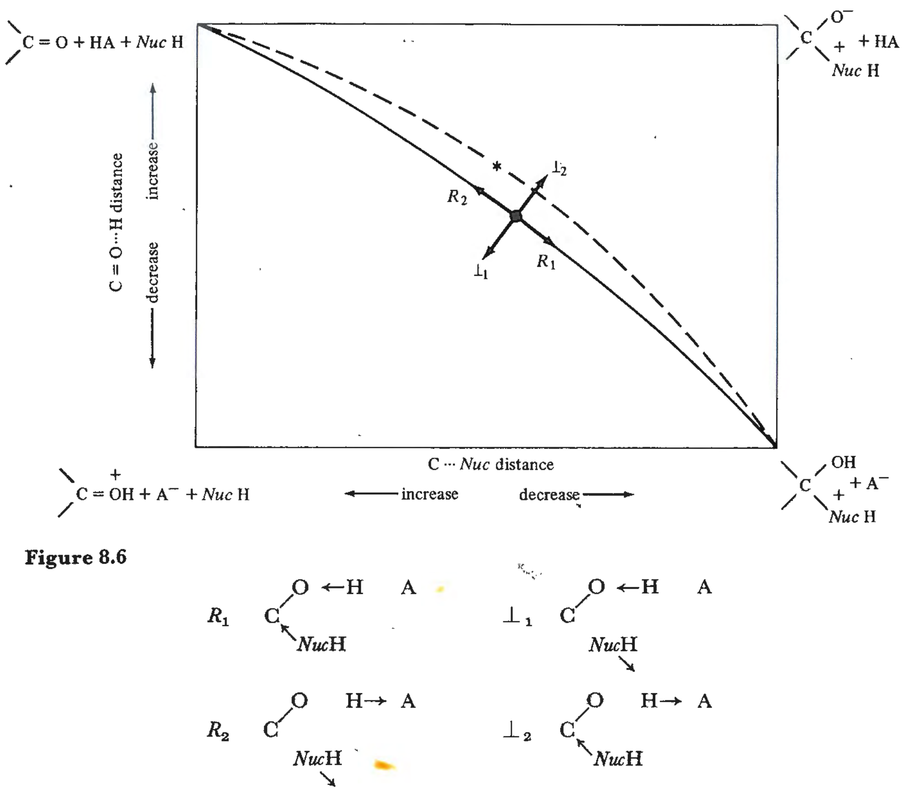
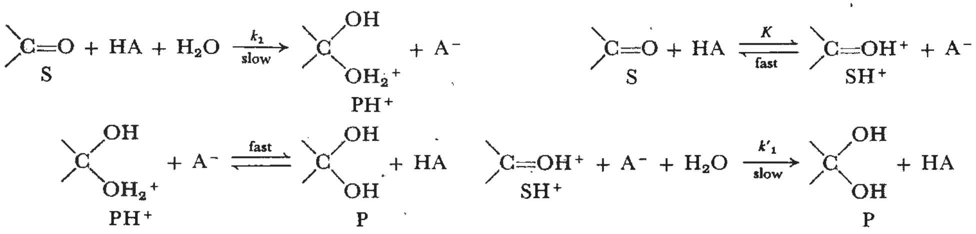


Figure 8.6

Projection in the horizontal plane of the three-dimensional reaction coordinate of the rate-determining step for Mechanism I, Scheme 5. Increasing nucleophilicity of *Nuc* will facilitate motions R_1 and $\perp_2$, causing shift of transition state to *.

SCHEME 5[25]

Mechanism I　　　　Mechanism II



$$\text{rate} = k_1[\text{S}][\text{HA}][\text{H}_2\text{O}]$$

$$\text{rate} = k_1'[\text{SH}^+][\text{A}^-][\text{H}_2\text{O}]$$

$$\text{SH}^+ = K\frac{[\text{S}][\text{HA}]}{[\text{A}^-]}$$

$$\text{rate} = k_1'K[\text{S}][\text{HA}][\text{H}_2\text{O}]$$

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[25] The mechanisms are abbreviated by incorporating the hydrogen bonding equilibria of Schemes 3 and 4 into the proton-transfer step, and simplified by neglecting reverse reactions in the slow steps.

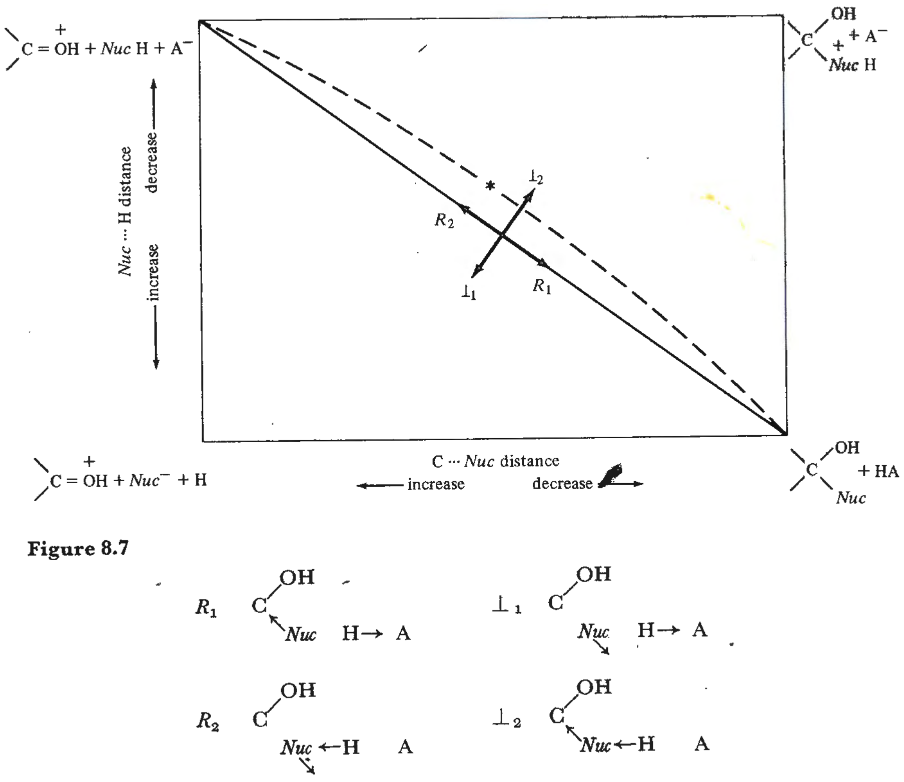

Figure 8.7

Projection of the reaction coordinate for the rate-determining step of Mechanism II, Scheme 5. Increasing nucleophilicity of *Nuc* will facilitate motions R_1 and $\perp_2$, shifting transition state to *.

to $K_{a_{\text{HA}}}^{-\beta}$ whereas K is equal to $K_{a_{\text{HA}}}/K_{a_{\text{SH}^+}}$, and the observed rate constant, $k_1'K$, is therefore proportional to $K_{a_{\text{HA}}}^{1-\beta} = K_{a_{\text{HA}}}^{\alpha}$. The mechanisms therefore also predict the same dependence of rate on strength of the acid catalyst. The fundamental reason for this kinetic equivalence is that the stoichiometric composition of the transition states in the rate-determining steps are the same in both mechanisms. We may summarize this conclusion by stating that general acid catalysis is not distinguishable by kinetic measurements alone from specific acid plus general base catalysis. The reader may show by similar reasoning (Problem 13) that general base catalysis cannot be distinguished from specific base plus general acid catalysis.

One method of deciding between Mechanisms I and II is to look at the trend of α in acid-catalyzed additions of various nucleophiles to a carbonyl group.[26] It follows from the reacting bond rules that in true general acid catalysis (Mechanism I), the sensitivity of the rate to acidity of the catalyst, and therefore also α, should decrease as the species adding is made more nucleophilic. The reason is that this variation will cause the change in reaction coordinate shown in

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[26] Jencks, *Catalysis in Chemistry and Enzymology*, pp. 195–197.

Table 8.2 DEPENDENCE OF BRØNSTED COEFFICIENT α ON BASICITY OF THE NUCLEOPHILE IN ADDITIONS TO C=O

Nucleophile	$pK_{a(NH^+)}$	Addition to	α
HOO^-	11.6	$\mathrm{ClC_6H_4\overset{O}{\overset{\|}{C}}H}$	0
RS^-	10	$\mathrm{CH_3\overset{O}{\overset{\|}{C}}H}$	0
$\phi NHNH_2$	5.2	$\mathrm{\phi\overset{O}{\overset{\|}{C}}H}$	0.2
$\mathrm{H_2N\overset{O}{\overset{\|}{C}}NH_2}$	0.2	$\mathrm{CH_3\overset{O}{\overset{\|}{C}}H}$	0.45
RSH	-7	$\mathrm{CH_3\overset{O}{\overset{\|}{C}}H}$	0.7
HOOH	-7	$\mathrm{ClC_6H_4\overset{O}{\overset{\|}{C}}H}$	1.0

SOURCE: W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969, p. 198, where a more extensive table may be found. Reproduced by permission of McGraw-Hill.

Figure 8.6, so that in the transition state the proton will be transferred from the catalyst to a smaller extent and the acidity of the catalyst will not be so strongly felt. If, on the other hand, the reaction is actually specific acid- plus general base-catalyzed, (Mechanism II, Scheme 5), then analysis of Figure 8.7 shows that the sensitivity of rate to basicity of A^-, and therefore also β, should decrease as the adding species is made more nucleophilic. But if this latter alternative were the correct mechanism and the reaction were erroneously regarded as a true general acid catalysis, one would find experimentally that α $(= 1 - \beta)$ would increase with more nucleophilic adding reagents.

The experimental evidence favors the conclusion that in addition of nucleophiles to carbonyl groups the observed catalysis is true general acid catalysis. Table 8.2 presents selected data; α decreases with increasing nucleophilicity of the addend. More specific techniques applicable to particular reactions lead to the same conclusion.[27] For hydration, Mechanism I of Scheme 5, with true general acid catalysis in the forward direction and specific acid plus general base catalysis in the reverse direction, thus appears to be the most reasonable one.

8.2 OTHER SIMPLE ADDITIONS

The previous section considered the simple single-step addition of water to the carbonyl group. Certain other nucleophiles undergo similar simple additions.

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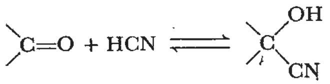
[27] See, for example, W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 63 (1964), p. 90.

Addition of Cyanide and Sulfite

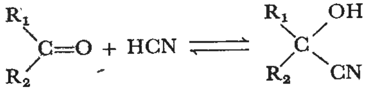
Aldehydes and unhindered aliphatic ketones or arylalkyl ketones add hydrogen cyanide to form cyanohydrins (Equation 8.22). As with hydration, the equilibrium lies farther to the right for aldehydes than for ketones. The equilibrium constant K is decreased by electron-donating groups, which stabilize the electron-deficient carbonyl carbon, and by the presence of bulky groups, which will be pushed closer together by the change to tetrahedral cyanohydrin. Table 8.3 gives selected equilibrium constants. The reaction is of considerable synthetic utility, since the cyano group is readily hydrolyzed to yield an α-hydroxy acid.

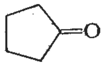
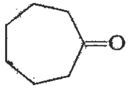
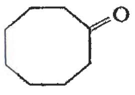


(8.22)

The cyanide addition was one of the first organic reactions to be elucidated mechanistically. In 1903 Lapworth found that whereas a high concentration of undissociated HCN is desirable to assure a high yield of cyanohydrin, the reaction

Table 8.3 EQUILIBRIUM CONSTANTS AT 20°C IN 96 PERCENT ETHANOL FOR THE REACTION



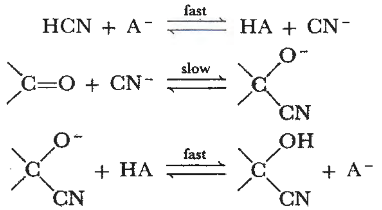
R_1	R_2	K	Reference
C_6H_5	H	220	*a*
p-$CH_3C_6H_5$	H	110	*a*
C_6H_5	CH_3	0.77	*b*
CH_3	CH_3	33	*b*
CH_3	C_2H_5	38	*b*
CH_3	i-C_3H_7	64	*b*
CH_3	t-C_4H_9	32	*b*
		48	*c*
		1000	*c*
		7.7	*c*
		1.16	*c*

[a] J. W. Baker, *Tetrahedron*, **5**, 135 (1959).
[b] A. Lapworth and R. H. F. Manske, *J. Chem. Soc.*, 1976 (1930).
[c] V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949).

rate depends on concentration of cyanide ion according to Equation 8.23.[28] His mechanism was essentially the same as the one accepted today (Scheme 6).[29]

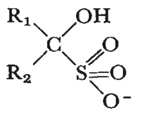
$$\text{rate} = k\left[\rangle C{=}O\right][CN^-] \qquad (8.23)$$

SCHEME 6



The reaction clearly should be subject to specific base catalysis, as is indeed observed. There is a possibility of general acid catalysis also; this process seems to be of only minor importance.[30]

Sulfite ions also undergo simple addition to aldehydes and unhindered ketones. No evidence for significant general catalysis exists, although a thorough search does not appear to have been made. Stewart and Donnally have investigated the mechanism in some detail; the situation is complicated by the multiple acid–base equilibria possible, but the reaction appears to follow the general pattern of other simple additions.[31] Equilibrium constants again show that the addition is more favorable with aldehydes than with ketones. The equilibrium constants (Table 8.4) correlate with the Taft σ^* inductive parameters.[32] The bisulfite adducts have been demonstrated by synthesis,[33] Raman spectroscopy,[34] and isotope effect measurements[35] to have the hydroxy sulfonic acid structure (2)



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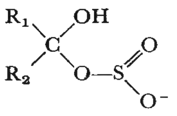

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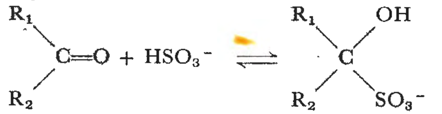
rather than the alternative hydroxy sulfite ester structure (3). Note that the softer sulfur center rather than the harder oxygen of the ambident sulfite prefers to be bonded to carbon.

Table 8.4 EQUILIBRIUM CONSTANTS AT 0°C FOR THE REACTION

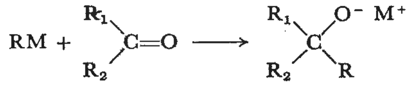


R_1	R_2	K^a
H	CH_3	800
CH_3	CH_3	200
CH_3	C_2H_5	40
CH_3	$i\text{-}C_3H_7$	8
CH_3	$t\text{-}C_4H_9$	1.6

[a] Calculated from data of K. Arai, *Nippon Kagaku Zasshi*, **82**, 955 (1961) [*Chem. Abstr.*, **56**, 5623g (1962)].

Addition of Organometallics

Addition of organometallics will not be considered in detail here; we wish merely to note that additions of organolithium and organomagnesium compounds are analogous to the processes that have been considered up to this point.[36] Although the detailed structure of these organometallics may vary from one compound to another, and may in some cases be unknown, they consist essentially of a strong, soft carbon Lewis base coordinated to a hard metal ion Lewis acid.[37] Combination



(8.24)

with a carbonyl compound (Equation 8.24) yields a bonding situation of so much lower energy that equilibrium constants are usually very large and the additions are for practical purposes irreversible. Acid–base catalysis of the type we have been considering is clearly out of the question here, as the reactions must be conducted under rigorously aprotic conditions if the organometallic reagent is not to be destroyed.

It should be noted that despite equilibria favorable to the adduct, the reactions are not without complications; because of the strongly basic properties of the organometallic, side reactions can occur. If the carbonyl compound bears α hydrogens, an enolate ion may result (Equation 8.25); the negative charge

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[28] A. Lapworth, *J. Chem. Soc.*, **83**, 995 (1903).

[29] The observation of a low yield of chiral cyanohydrin when certain optically active amines are present requires a minor modification of the mechanism to allow for coordination of the carbonyl oxygen with a cation. See V. Prelog and M. Wilhelm, *Helv. Chim. Acta*, **37**, 1634 (1954); H. Hustedt and E. Pfeil, *Justus Liebigs Ann. Chem.*, **640**, 15 (1961).

[30] (a) W. J. Svirbely and J. F. Roth, *J. Amer. Chem. Soc.*, **75**, 3106 (1953); (b) W. J. Svirbely and F. H. Brock, *J. Amer. Chem. Soc.*, **77**, 5789 (1955).

[31] (a) T. D. Stewart and L. H. Donnally, *J. Amer. Chem. Soc.*, **54**, 2333, 3555, 3559 (1932); (b) see also D. A. Blackadder and C. Hinshelwood, *J. Chem. Soc.*, 2720 (1958).

[32] K. Arai, *Nippon Kagaku Zasshi*, **82**, 955 (1961) [*Chem. Abstr.*, **56**, 5623g (1962)].

[33] (a) W. M. Lauer and C. M. Langkammerer, *J. Amer. Chem. Soc.*, **57**, 2360 (1935); (b) R. L. Shriner and A. H. Land, *J. Org. Chem.*, **6**, 888 (1941).

[34] C. N. Caughlan and H. V. Tartar, *J. Amer. Chem. Soc.*, **63**, 1265 (1941).

[35] W. A. Sheppard and A. N. Bourns, *Can. J. Chem.*, **32**, 4 (1954).

[36] The mechanisms are complex, particularly in the organomagnesium (Grignard) reactions. Several reactive species are present, and the product metal alkoxide can complex with unreacted organometallic. Furthermore, trace transition metal impurities in the magnesium used to prepare Grignard reagents appear to facilitate electron transfer and may cause the reaction to proceed at least partly by a radical pathway. See (a) J. Laemmle, E. C. Ashby, and H. M. Neumann, *J. Amer. Chem. Soc.*, **93**, 5120 (1971); (b) E. C. Ashby, J. Laemmle, and H. M. Neumann, *Accts. Chem. Res.*, **7**, 272 (1974).

[37] In some other organometallics, for example the soft acid–soft base organomercury compounds, the carbon–metal bond has a high degree of covalent character and is sufficiently strong that these substances are considerably less reactive than substances of the organolithium or organomagnesium type.