The Mandelaldehyde–2-Hydroxyacetophenone Isomerization[1]

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Abstract: As a model system for gaining information about the glyceraldehyde-dihydroxyacetone isomerization, the interconversion of mandelaldehyde and 2-hydroxyacetophenone has been studied. Using mandelaldehyde (**3a**) and deuteriomandelaldehyde (**3b**), isolated and added to the reaction mixture in the form of the dimers (**1a** and **1b**), with anhydrous pyridine and aqueous pyridine (H_2O and D_2O) as the basic catalyst, evidence has been adduced to support the generally accepted enolization mechanism for the isomerization. The rate of the reaction shows a dependence on protic species, including the substrates and products themselves and is in accord with the expression rate = $(\Sigma k_i[HA]_i)$ [mandelaldehyde dimer] [pyridine]. A deuterium isotope effect of *ca.* 1.3 is observed which, when corrected for the apparently differing amounts of aldehyde form (presumably **2a** and **2b**) in equilibrium with the proteo dimer (**1a**) and the deuterio dimer (**1b**), gives a value of *ca.* 3.9. From the rates of isomerization of *p*-methoxy-, *p*-methyl-, *p*-chloro-, and *p*-trifluoromethylmandelaldehyde (used as the dimers) a Hammett ρ constant of 1.4 ± 0.1 is calculated. The observed rates with trifluoroethanol, 2-pyridone, phenol, 2-hydroxymethylpyridine, 2-(β-hydroxyethyl)pyridine, 2-(γ-hydroxypropyl)pyridine, and benzoic acid indicate a Brønsted catalytic constant of 0.11–0.15 if the difference in pK_a values between water and pyridine solution is taken into account. Benzamidine was found to be a very much more effective catalyst than other bases of comparable basicity or other acids of comparable or greater acidity. Although these data do not allow a clean choice between the ring-opening step and the enolization step as the rate-determining event, the latter is considered to be more likely and is thought to require both a base (*i.e.*, pyridine) and an acid (*e.g.*, a protic species) catalyst.

The reactions of the trioses glyceraldehyde and dihydroxyacetone and their corresponding phosphates have provided a focal point for the investigation of enzyme model catalysts in this laboratory.[3] Among the several *in vivo* reactions that these compounds undergo is an aldo–keto interconversion catalyzed by the enzyme triosephosphate isomerase. An intriguing goal, therefore, is the design of a polyfunctional compound that mimics *in vitro* the action of this enzyme. Preliminary to pursuing this goal in the trioses, however, a study has been carried out in a system involving less amphisbaenic molecules than dihydroxyacetone; *viz.*, mandelaldehyde and 2-hydroxyacetophenone.

The aldo–keto interconversion, first described by Lobry de Bruyn and Alberda van Eckenstein,[4] is represented by numerous examples both in *in vivo*[5] and *in vitro*[6] systems. As early as 1900 an enediol mechanism was postulated for the reaction,[7] and further detail was added a decade later by the suggestion that the formation of the enediol is initiated by direct removal of an α-proton.[8] The enolization pathway has gained considerable support from more recent investigations using isotopically substituted sugars.[9] Reactions bearing some resemblence to the aldo–keto interconversion (Lobry de Bruyn–Alberda van Eckenstein isomerization), however, are known to involve a hydride shift pathway as, for example, the conversion of D-glucose 3-phosphate to 3-deoxy-D-glucosulose.[10] Similar pathways are also characteristic of the Cannizzaro reaction, the enzymatic oxidation of aldehydes to esters, and the base-catalyzed rearrangements of α-dicarbonyl compounds.[11] The hydride shift mechanism for the aldo–keto interconversion cannot be categorically excluded on the basis of the data in the literature and, indeed, a tritiated sample of D-fructose 6-phosphate has been enzymatically converted to D-glucose 6-phosphate with only partial loss of the tritium and intramolecular transfer of the remainder to the adjacent carbon.[9j-9l] This result has been interpreted in terms of an enolization pathway and enzyme-bound tritium intermediates but is also consistent with a combined enolization–hydride shift mechanism.

Attention in this laboratory was directed to the hydride shift mechanism as a possible explanation for the observation that in aqueous pyridine glyceraldehyde and dihydroxyacetone undergo aldol condensation to hexoses,[3] whereas in anhydrous pyridine they only undergo aldo–keto isomerization.[12] To minimize the complication of side reactions, the mandelaldehyde–2-hydroxyacetophenone system rather than the glycer-

(1) Presented, in part, at the Midwest Regional Meeting of the American Chemical Society, Kansas City, Kan., Oct 29–30, 1969.

(2) National Aeronautics and Space Administration predoctoral trainee, 1966–1969; National Science Foundation predoctoral trainee, 1969–1970.

(3) C. D. Gutsche, D. Redmore, R. S. Buriks, I. Nowotny, H. Grassner, and C. W. Armbruster, *J. Amer. Chem. Soc.*, **89**, 1235 (1967).

(4) C. A. Lobry de Bruyn and W. Alberda van Eckenstein, *Recl. Trav. Chim. Pays-Bas*, **14**, 203 (1895).

(5) *Cf.* review by Y. J. Topper in "The Enzymes," Vol. 5, P. D. Boyer, H. Lardy, and K. Myrbäck, Ed., Academic Press, New York, N. Y., 1961, Chapter 26.

(6) *Cf.* reviews by H. S. Isbell, H. L. Frush, C. W. R. Wade, and C. E. Hunter, *Carbohydr. Res.*, **9**, 163 (1969), and J. C. Speck, *Advan. Carbohydr. Chem.*, **13**, 63 (1958).

(7) A. Wohl and C. Neuberg, *Chem. Ber.*, **33**, 3900 (1900).

(8) L. Michaelis and P. Rona, *Biochem. Z.*, 47, 447 (1912).

(9) (a) J. C. Sowden and R. Schaffer, *J. Amer. Chem. Soc.*, **74**, 499, 505 (1952); (b) Y. J. Topper and D. Stetten, *J. Biol. Chem.*, **189**, 191 (1951); (c) Y. J. Topper, *ibid.*, **225**, 419 (1957); (d) B. Bloom and Y. J. Topper, *Science*, **124**, 982 (1956); (e) B. Bloom and Y. J. Topper, *Nature (London)*, **181**, 1128 (1958); (f) R. Bentlen and D. S. Bhate, *J. Biol. Chem.*, **235**, 1225 (1960); (g) H. S. Isbell and C. W. R. Wade, *J. Res. Nat. Bur. Stand., Sect. A*, **71**, 137 (1967); (h) M. W. McDonough and W. A. Wood, *J. Biol. Chem.*, **236**, 1220 (1960); (i) S. V. Rieder and I. A. Rose, *Fed. Proc.*, **15**, 337 (1956); (j) I. A. Rose and E. L. O'Connell, *Biochem. Biophys. Acta*, **42**, 159 (1960); (k) I. A. Rose and E. L. O'Connell, *J. Biol. Chem.*, **236**, 3086 (1961); (l) S. V. Rieder and I. A. Rose, *ibid.*, **234**, 1007 (1959); (m) I. A. Rose, *Brookhaven Symp. Biol.*, **15**, 293 (1962); (n) I. A. Rose, E. L. O'Connell, and R. P. Mortlock, *Biochem. Biophys. Acta*, **178**, 376 (1969); (o) H. S. Isbell, H. L. Frush, C. W. R. Wade, and C. E. Hunter, *Carbohydr. Res.*, **9**, 163 (1969).

(10) G. Fodor and J. P. Sachetto, *Tetrahedron Lett.*, 401 (1968).

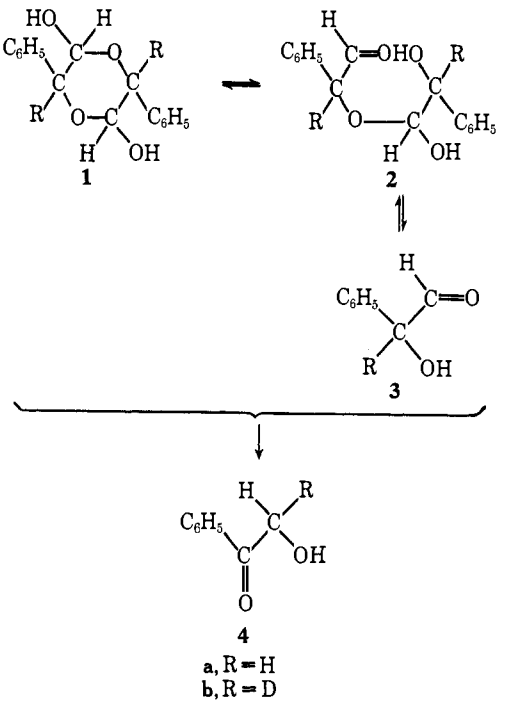
(11) *Cf.* W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 157–158.

(12) H. O. L. Fischer, C. Taube, and E. Baer, *Chem. Ber.*, 60, 479 (1927).

aldehyde–dihydroxyacetone system has been chosen to study this isomerization.

Results and Discussion

Isotope Studies. When a solution of mandelaldehyde (**3**)[13] (present in solution almost entirely as the cyclic dimer **1** along with a small amount of an aldehyde that is assumed to be **2**) is heated for several hours in pyridine solution essentially complete conversion to monomeric 2-hydroxyacetophenone (**4**) occurs. The progress of the isomerization can be followed by using perdeuteriopyridine as the solvent and noting the changes in the nmr spectrum as the complex pattern of the mandelaldehyde dimer (between 5.05 and 6.12 ppm) changes to the singlet resonance at 5.18 ppm characteristic of the 2-hydroxyacetophenone. An internal standard for determining the concentration of 2-hydroxyacetophenone is also provided by the downfield portion of its aromatic multiplet which is well separated from the mandelaldehyde resonances. Thus, with deuteriomandelaldehyde dimer (**1b**) as the substrate it is possible to determine the hydrogen–deuterium content at C-2 of 2-hydroxyacetophenone not only at complete reaction but at intermediate points as well by measuring the area of the methylene singlet resonance relative to the aromatic resonance. Employing this method, five reactions were studied at 30°: (a) mandelaldehyde dimer (**1a**) in anhydrous pyridine, (b) deuteriomandelaldehyde dimer (**1b**) in anhydrous pyridine, (c) mandelaldehyde dimer (**1a**) in pyridine + H_2O, (d) deuteriomandelaldehyde dimer (**1b**) in pyridine + H_2O, (e) mandelaldehyde dimer (**1a**) in pyridine + D_2O. The product from reactions a, c, and d was proteo-2-hydroxyacetophenone (**4a**), and the product from reactions b and e was monodeuterio-2-hydroxyacetophenone (**4b**). From these results it is clear that the isomerization proceeds with complete exchange of carbon-bound deuterium (hydrogen) for hydrogen (deuterium) from the solvent. Although these results are in accord with an enolization pathway (in which the α-hydrogen is labilized as a proton), a hydride shift pathway cannot be excluded, for exchange prior to or subsequent to isomerization might obscure the interpretation. That reaction e proceeds with the incorporation of a maximum of one deuterium atom per molecule of product does, however, seem to eliminate exchange after isomerization. This was confirmed by the observation that 2-hydroxyacetophenone incorporates deuterium at least ten times more slowly than the isomerization takes place. Exchange prior to the isomerization was also ruled out by (a) the isolation of mandelaldehyde dimer from partially isomerized material (pyridine + D_2O) containing no carbon-bound deuterium and (b) the invariant line shape of the aldehyde resonance in the nmr during the course of the reaction when either mandelaldehyde (with D_2O) or deuteriomandelaldehyde (with H_2O) was used as starting material (see Figures 6 and 7); if exchange preceded isomerization the character of this resonance should change from doublet to broadened singlet or triplet in the first case and from broadened singlet or triplet to a doublet in the second case. These results, then, appear to exclude a hydride shift pathway and to support a mechanism in which enolate anions lie on the reaction coordinate for the isomerization.



Kinetic Measurements. Although the intense absorption by 2-hydroxyacetophenone at 242 nm allows the isomerization to be followed by uv spectral determinations, the necessity for removing pyridine prior to the determination reduces the accuracy of this method. In spite of the lower inherent accuracy of the nmr method, it was chosen as the better alternative, the reactions being conveniently run in degassed solutions in sealed tubes in the probe of the nmr spectrometer.

Employing the nmr method, reaction rates for the isomerization of mandelaldehyde dimer in pyridine solution were determined under a variety of experimental conditions. In all cases, pseudo-first-order plots were obtained to greater than 85% reaction from which rate constants were calculated with a precision of ±2% for data from a single run and, in most cases, ±5% for data from replicate runs. All of these data could be fit to the expression

$$\text{rate} = d[\mathbf{4}]/dt = -2[\mathbf{1}]/dt = k_{obsd}(a_0 - [\mathbf{4}])$$

where a_0 is the equivalent concentration of mandelaldehyde species (**1**, **2**, **3**) at zero time or of 2-hydroxyacetophenone (**4**) at infinity time. Thus, the quantity (a_0 − [**4**]) is the equivalent concentration of mandelaldehyde species remaining at time t and includes the concentrations of mandelaldehyde cyclic dimer (**1**), open chain dimer (**2**), and monomer (**3**). Hereafter the term "mandelaldehyde" will be used to denote the sum of all mandelaldehyde species, and the specific species will be denoted explicitly by name and/or number (*i.e.*, **1**, **2**, or **3**). The observed first-order dependence on mandelaldehyde, however, indicates that the reacting entity is either the monomer (**3**) or the dimer (**1** and/or **2**) but not both. Since nmr clearly indicates that the dimeric structure is retained in solution, the observed reaction rate therefore reduces to a first-order dependence on the concentration of dimeric mandelaldehyde. Although this presents the possibility that the rate-determining process in the isomerization may

(13) D. W. Griffiths and C. D. Gutsche, *J. Org. Chem.*, in press.

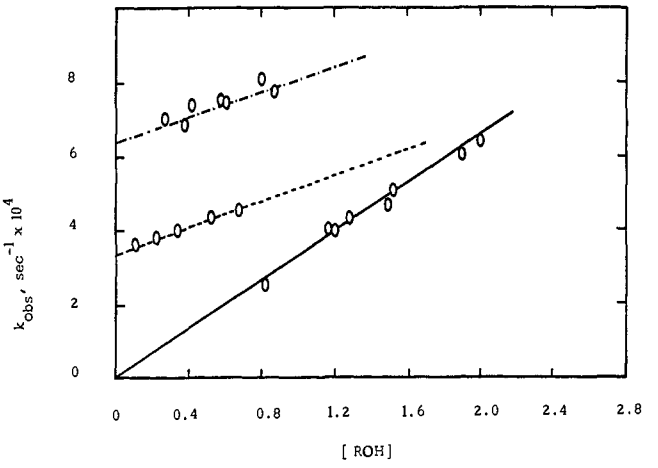


Figure 1. The dependence of the pseudo-first-order rate constant for the isomerization of mandelaldehyde in pyridine at 90° on the total substrate plus product concentration (——), on water concentration with mandelaldehyde concentration = 0.1 N (- - - - - -), and on water concentration with mandelaldehyde concentration = 0.2 N (- · - · - · -).

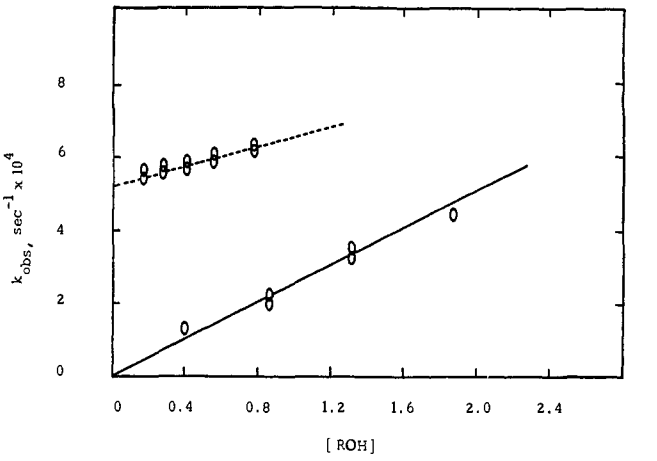


Figure 2. The dependence of the pseudo-first-order rate constant for the isomerization of 1-deuteriomandelaldehyde in pyridine at 90° on the equivalent concentration of the substrate plus product (——) and on the molar concentration of water (- - - - - - - -).

be the dedimerization of cyclic mandelaldehyde dimer (**1**), the data to be discussed seem better interpreted in terms of a rate-determining enolization of the open-chain dimer (**2**), shown by nmr to be present to the extent of *ca.* 5% in equilibrium with the cyclic dimer (**1**).

Rate constants for isomerizations carried out in anhydrous pyridine varied linearly from 2.46 to 6.40 × 10^{-4} sec^{-1} as the starting concentration of mandelaldehyde (calculated as monomer) was varied from 0.82 to 2.00 M, as illustrated in Figure 1. Thus, rate = k_{obsd} [mandelaldehyde] where $k_{obsd} = k_{cat}$[ROH] where ROH is the total concentration of hydroxylic species in solution and, in this instance is equal to 2[**1** + **2**] + [**3**] + [**4**] which is a constant value. Clearly, the substrate itself is acting as a catalyst; extrapolation of the observed rate constants to zero ROH concentration gives a value of zero, suggesting that self-catalysis is, in fact, obligatory for isomerization to occur in anhydrous pyridine. Self-catalysis has also been observed in the mutarotation of tetramethylglucose in benzene and pyridine[14] and tetraacetylglucose and glucose in anhydrous pyridine.[15,16] It is reasonable to suppose that in all of these cases pyridine is acting as a basic catalyst and the ROH species as an acidic catalyst. In the present instance, assuming the rate-determining step to be the enolization of the open chain dimer (**2**), this can be accommodated by the reactions

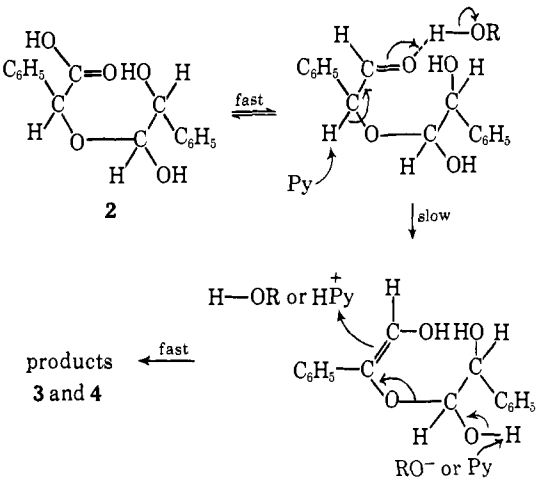
$$2 + \mathrm{ROH} \overset{K}{\rightleftharpoons} (2\cdot\mathrm{ROH})$$

$$(2\cdot\mathrm{ROH}) + \mathrm{Py} \xrightarrow{k} \text{products}$$

and depicted as shown in Scheme I. It must be assumed that the effectiveness of **1**, **2**, **3**, and **4** as acid catalysts is approximately equal.

Rate constants for isomerization carried out in aqueous pyridine containing mandelaldehyde in 1.0 and 2.0 M concentration (calculated as monomer) are plotted in Scheme I, these results fitting the expression rate = k_{obsd}[mandelaldehyde] where $k_{obsd} = k_{cat}$[ROH] + k_h[H_2O]. The intercepts of these lines (*i.e.*, H_2O = 0) should coincide with the rate constants for 1.0 and 2.0 M solutions of mandelaldehyde in anhydrous pyridine, and excellent agreement was observed in this respect. A comparison of the rate constants for catalysis by water and by the substrates themselves (*i.e.*, **1**, **2**, **3**, and **4**) indicates that water is a somewhat less efficient catalyst. This correlates with the relative acidities of water (pK_a = 15.3) and compounds **1**–**4** ($pK_a \sim$ 12–13) and is in agreement with the concept of a general acid catalyzed process.

Scheme I. General Base-General Acid Catalyzed Isomerization of Mandelaldehyde



Deuterium Isotope Effects. Rate measurements similar to those described above were obtained with 1-deuteriomandelaldehyde as the substrate, and the data shown in Figure 2 for reactions carried out in anhydrous pyridine and aqueous pyridine were obtained. Employing the kinetic expressions that have been discussed above, rate constants for self-catalysis and for H_2O catalysis were obtained and compared with the values obtained with 1-proteomandelaldehyde as the substrate, as shown in Table I.

(14) C. G. Swain and J. F. Brown, *J. Amer. Chem. Soc.*, 74, 2534 (1952).
(15) A. M. Eastham, E. L. Blackhall, and G. A. Latremouille, *ibid.*, 77, 2182 (1955).
(16) A. S. Hill and R. S. Shallenberger, *Carbohydr. Res.*, 11, 541 (1969).

Table I. Deuterium Isotope Effects

Method of calcn	k_h, M^{-1} sec^{-1}	k_d, M^{-1} sec^{-1}	k_h/k_d
Rate constants for self-catalysis	$3.2 \pm 0.2 \times 10^{-4}$	$2.4 \pm 0.2 \times 10^{-4}$	1.3 ± 0.1
Rate constants for H_2O catalysis	$1.6 \pm 0.3 \times 10^{-4}$	$1.3 \pm 0.1 \times 10^{-4}$	1.2 ± 0.3

An isotope effect of 1.3 is lower than anticipated for an enolization process but commensurate with a rate-determining ring opening of a compound in which the deuterium is at a position β to the reacting center.[17] The small, yet measurable, amount of aldehyde (presumably **2**) in equilibrium with the dimer (**1**), however, would seem to negate the ring opening as the rate-determining step and implicate the enolization step.

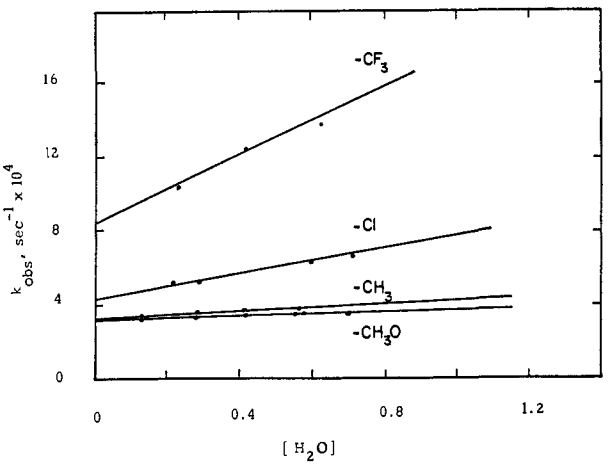


Figure 3. The dependence of the pseudo-first-order rate constants for the isomerization of substituted mandelaldehydes on the molar concentration of water (initial concentration of mandelaldehyde = 1.0 *N*).

That the true deuterium isotope effect may, in fact, be larger than 1.3 and, thus, be in closer accord with the enolization pathway is indicated by the equilibrium constant for the interconversion of cyclic dimer **1** and the open chain dimer **2** for the proteo and deuterio analogs. Comparison of the areas of the aldehyde resonances in the nmr of 1-deuteriomandelaldehyde and proteomandelaldehyde indicates that there is an inverse isotope of *ca.* 3 for the ring opening, *i.e.*, $K_{(1,2)\text{-}d}/K_{(1,2)\text{-}h} = 3$, indicating that the concentration of "free" aldehyde is three times greater for the deuterated species than for the nondeuterated species. Thus, the true isotope effect presumably should be $k_h/k_d = (K_{(1,2)\text{-}d}/K_{(1,2)\text{-}h})(k_{\text{obsd h}}/k_{\text{obsd d}}) = 3.9$. This is a far greater isotope effect than would be expected for an equilibrium of this sort, however, and this difference in equilibrium constant, apparently due to the substitution of deuterium for hydrogen, must be viewed with some skepticism.

Hammet Correlation. Employing the nmr method described above, the isomerization rates in aqueous pyridine were measured for *p*-methoxy-, *p*-methyl-, *p*-chloro, and *p*-trifluoromethylmandelaldehydes.[13] These were found in all cases to be first order in the total mandelaldehyde concentration and to obey the same rate law that has been discussed above, yielding the data shown in Figure 3. The values of k_h, the pseudo-bimolecular rate constants for water catalysis, were determined from the slopes of the linear least squares lines of best fit and, when plotted against the appropriate Hammett σ values,[18] gave the plot shown in Figure 4 from which a Hammett ρ constant of 1.4 ± 0.1 was calculated.

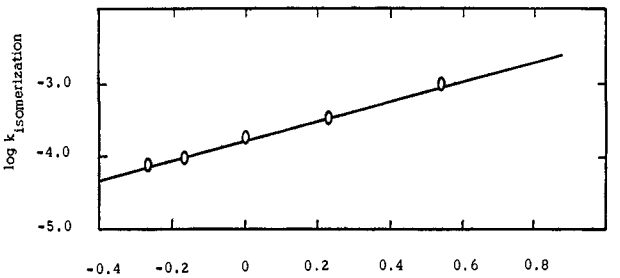


Figure 4. Hammett ρ-σ correlation.

The positive ρ value is in accord with a mechanism in which negative charge is generated adjacent to or near the aromatic ring in the transition state. The ionization of 1-aryl-1-nitroethanes may be viewed as a model for rate-determining enolization of mandelaldehyde. For a series of substituted arylnitroethanes, the ρ value, calculated from deprotonation rates in 50% (v/v) H_2O–MeOH, is reported to be 1.44.[19] This is in excellent agreement with the ρ value observed in the present work and provides additional support for the rate-determining enolization pathway. If ring opening were rate determining a considerably lower ρ value would be expected based on the value of 0.56 reported for the ionization of phenylacetic acids in water,[20] a reaction which may be viewed as a model for the ring opening process.

Brønsted Correlation. If the mandelaldehyde–2-hydroxyacetophenone isomerization is subject to general acid catalysis, a correlation between the strength of the acid catalyst and the rate of the reaction should be observed, and Brønsted plots[21] should be obtained. The rate does, indeed, increase as the acid strength of the catalyst increases, but construction of Brønsted plots is complicated by the fact that the dissociation constants in pyridine solution are not available for all of the catalysts that were used. Assuming that (a) the relative acidities of all of the catalysts used (all of the same charge type) are independent of solvent[22] and (b) the acidities of phenol, 2-pyridone, and 2,2,2-trifluoroethanol are increased by 2.5–3.4 pK units

(17) *Cf.* L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960, Chapter 5.

(18) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 173.

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

(20) P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968, p 12.

(21) J. N. Brønsted and K. J. Pederson, *Z. Physikal. Chem.*, **108**, 185 (1924).

(22) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, p 108.

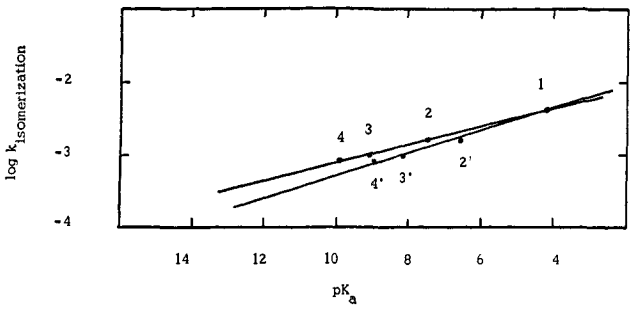


Figure 5. Brønsted correlation: 1, benzoic acid; 2, phenol (pK_a correction 2.5); 2′, phenol (pK_a correction 3.4); 3, 2-pyridone (pK_a correction 2.5); 3′, 2-pyridone (pK_a correction 3.4); 4-trifluoroethanol (pK_a correction 2.5); 4′, trifluoroethanol (pK_a correction 3.4).

relative to benzoic acid in pyridine solution,[23] a Brønsted coefficient of 0.11–0.15 was obtained as shown in Figure 5.

If it is assumed that the Brønsted coefficient is a measure of the change in the charge on the proton-donating or proton-accepting group in the transition state[24] the low value in the present case suggests that proton transfer has occurred to a rather small extent from the general acid to the substrate. Either a rate-determining enolization or ring opening process can be accommodated to this result.

Catalysis by Benzamidine. Pursuant to the goal of designing polyfunctional catalysts for the aldo–keto isomerization several bifunctional molecules were tested including, in addition to 2-pyridone and benzoic acid (see above), 2-hydroxymethylpyridine, 2-(β-hydroxyethyl)pyridine, and 2-(γ-hydroxypropyl)pyridine. In no cases were abnormal effects noted. Benzamidine, on the other hand, proved to be an unusually effective catalyst. The pseudobimolecular catalytic rate constant, determined from the slope of the linear least squares line of best fit, is 0.48 ± 0.04 M^{-1} sec^{-1}, a value that is more than 120-fold greater than the rate constant for catalysis by benzoic acid. Whether benzamidine is acting as a bifunctional catalyst or simply as a particularly effective nucleophilic catalyst (pK_a = 11.6[25]) is not yet known. That it is a better catalyst than other bases of comparable strength, however, is indicated by the fact that solutions of mandelaldehyde in diethylamine (pK_a = 10.93[25]), and in piperidine (pK_a = 11.22[25]) are stable for several hours at room temperature, whereas the isomerization is essentially complete within minutes in pyridine solutions containing 0.5 M benzamidine. Work is currently in progress to determine the basis for the catalytic action of benzamidine.

Experimental Section

General Procedure for Preparation of Nmr Samples. For the preparation of anhydrous samples, a dry tube (Wilmad 504-GP frosted medium wall nmr tube attached to a 10/30 joint and cleaned, prior to using, by chromic acid treatment followed by ten washings with distilled water and 12 hr of drying at 110°) containing a weighed amount of mandelaldehyde dimer was attached to an all-glass vacuum manifold. After evacuation, *ca.* 0.4 ml of anhydrous pentadeuteriopyridine containing 0.01 ml of cyclohexane was distilled directly from calcium hydride into the sample tube. The reaction mixture was degassed by three or more freezing–evacuation–thawing cycles, and the tube was sealed off at 0.001 mm. The total weight of the sample was determined by the difference in weights between the filled and empty sample tube. Concentrations by weight were calculated from the known amount of mandelaldehyde used and the total sample weight, and these were converted to a molar scale by means of previously determined densities of solutions of mandelaldehyde in anhydrous pyridine.

For the preparation of aqueous solutions, a weighed amount of mandelaldehyde was placed in a 50-ml round-bottomed flask, and an amount of pyridine sufficient to produce a 2.3–2.5 M solution of mandelaldehyde monomer was weighed in. The mixture was degassed, warmed to 60° for 30 min to dissolve the mandelaldehyde, cooled to room temperature, and filtered through a sintered glass disk. Accurately weighed samples from this stock solution were transferred to 2-ml volumetric flasks, an appropriate amount of water was added, the solutions were diluted to volume with anhydrous pyridine, and 0.40-ml aliquots were transferred to nmr sample tubes which were handled as described above.

Isomerization Reaction. To assess the general course of the reaction an initial nmr spectrum was obtained, the sample was immersed in a constant-temperature bath maintained at 90 ± 0.05°, and it was removed at measured intervals and subjected to nmr analysis. At intermediate reaction times all of the resonances could be assigned either to mandelaldehyde dimer or to 2-hydroxyacetophenone, but at the completion of the reaction those which were originally assigned to mandelaldehyde dimer had disappeared and the spectrum was that of 2-hydroxyacetophenone: nmr ($CDCl_3$) δ 5.18 (s, 2, CH_2), 6.48 (s, 1, OH), 7.44–8.20 ppm (m, 5, ArH). Continuation of the reaction well beyond the time necessary for complete conversion to 2-hydroxyacetophenone (3 weeks at 90°) indicated that no decomposition of the product occurred. Identical results were obtained for isomerization carried out in either anhydrous or aqueous pyridine solutions.

Deuterium Exchange Experiments. Samples were placed in a water bath maintained at 30° and removed at measured intervals for nmr analysis. The hydrogen–deuterium content at the methylene carbon of 2-hydroxyacetophenone was calculated from the ratio of the area of the methylene singlet to the area of the extreme downfield resonance of the aromatic protons of 2-hydroxyacetophenone. The reactions were followed for at least 10 half-lives, and the results shown in Table II were obtained.

Table II. Hydrogen–Deuterium Content of Products from **1a** and **1b**

Reactant	Solvent	Product	Hydrogen content at C-2 of product **4**
1a	Anhydrous pyridine	**4a**	1.9
1b	Anhydrous pyridine	**4b**	1.2
1a	Pyridine + H_2O	**4a**	1.9
1b	Pyridine + H_2O	**4a**	1.9
1a	Pyridine + D_2O	**4b**	1.1

Mandelaldehyde dimer was recovered from a partially isomerized sample in the following fashion. A 2.0-g sample of mandelaldehyde dimer was treated with 3.0 g (0.15 mol) of D_2O and 18 g of pyridine, and the sample was heated to 70° for 10 min to dissolve the mandelaldehyde and then held for 3.5 hr at 30°. Removal of the solvent at reduced pressure, treatment of the oily residue with benzene–*n*-heptane followed by evaporation, and trituration of the dry powder with acetone gave 0.4 g of recovered mandelaldehyde as a white powder: mp 160–163°; ir (KBr) 3550 (OH), 2550 (OD), 1140 cm^{-1} (COC); nmr (degassed DMSO) 5.20 (d, J = 2.0 Hz superimposed on d of d, 2, CHCHOH and CHCHOD), 5.37 (d, 2, J = 2.0 Hz, CHCHOH and CHCHOD), 6.30 (d, 0.7, J = 5.0 Hz), 7.21–7.59 ppm (m, 10, ArH).

Although a solution of mandelaldehyde dimer in DMSO or pyridine shows no resonance in the nmr for a free aldehyde group, at room temperature at 90° the resonance is clearly discernible at 10.03 ppm as a doublet (J = 1.5 Hz) in **1a** and a singlet in **1b**. The

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(24) Reference 11, p 241.

(25) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, p 140.

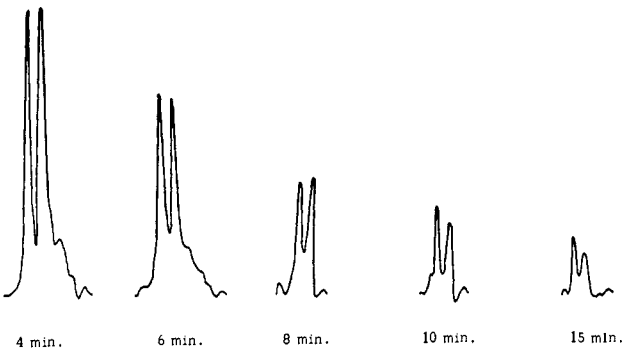

Figure 6. Nmr spectrum of mandelaldehyde in pyridine-d_5–D_2O as a function of reaction time; aldehyde resonance.

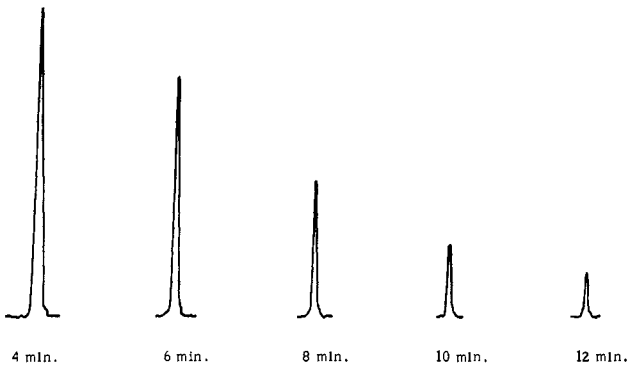

Figure 7. Nmr spectrum of 1-deuteriomandelaldehyde in pyridine-d_5–H_2O as a function of reaction time; aldehyde resonance.

shapes of the aldehyde resonances of **1a** and **1b** in anhydrous pyridine at various reaction times are shown in Figures 6 and 7.

General Procedure for Kinetic Measurements. Using a Varian Model A-60A nmr spectrometer equipped with a Varian Model V-6040 variable-temperature controller, reaction rates were determined by electronic integration of the methylene singlet of 2-hydroxyacetophenone at 5.18 ppm as a function of time. The runs at 90 ± 1° were conducted in the probe of the nmr spectrometer, and the temperature was measured by means of the difference in chemical shift between the methylene and hydroxyl signals of ethylene glycol.[26] Each measurement consisted of two integrations, one in the forward and one in the reverse sweep mode. Frequent measurements were made over a period of 2 or more half-lives, and an infinity measurement was made after 5 or more half-lives.

For a first-order reaction the integrated rate law is given by the expression $\ln [a/(a - x)] = k_{obsd}t$ where a is the initial equivalent concentration of reactant and x is the decrease in that concentration which has occurred at time t. In the present work the value of x was determined by the nmr method described above, and the pseudo-first-order rate constant, k_{obsd}, was obtained from a plot of $\log (a - x)$ against t where a was determined experimentally from the value of x at "infinity" time. All plots have been analyzed by means of a least squares program[27] written for the Hewlett-Packard Model 9100A calculator, and the uncertainty in the rate constants has been determined from the standard deviation of the slope of the least squares line.

Table III

[Mandelaldehyde], M (calcd as **3a**)	k_{obsd}, sec^{-1}
0.82	2.46×10^{-4}
1.17	3.97×10^{-4}
1.20	3.96×10^{-4}
1.29	4.24×10^{-4}
1.49	4.66×10^{-4}
1.51	5.02×10^{-4}
1.90	6.02×10^{-4}
2.00	6.40×10^{-4}

Table IV

[Mandelaldehyde], M (calcd as **3a**)	[H_2O], M	k_{obsd}, sec^{-1}
1.0	0.122	3.56×10^{-4}
	0.216	3.75×10^{-4}
	0.342	3.95×10^{-4}
	0.533	4.27×10^{-4}
	0.678	4.60×10^{-4}
2.0	0.257	6.94×10^{-4}
	0.390	6.75×10^{-4}
	0.586	7.44×10^{-4}
	0.610	7.34×10^{-4}
	0.801	8.06×10^{-4}

(26) Varian Associates, Palo Alto, Calif., Publication No. 87-202-001, p 26.

(27) We are indebted to Professor J. L. Kurz for this program.

Rate Dependence on Initial Concentration. Isomerizations of **1a** in anhydrous pyridine at 90° at various initial concentrations produced the values shown in Table III (see Figure 1).

Table V

[Deuteriomandelaldehyde], M (calcd as **3b**)	[H_2O], M	k_{obsd}, sec^{-1}
0.40	0.00	1.23×10^{-4}
0.86	0.00	2.18×10^{-4}
1.31	0.00	3.42×10^{-4}
1.76	0.00	4.39×10^{-4}
2.00	0.158	5.37×10^{-4}
2.00	0.267	5.62×10^{-4}
2.00	0.406	5.68×10^{-4}
2.00	0.550	5.86×10^{-4}
2.00	0.770	6.20×10^{-4}

Table VI

Para substituent	[H_2O], M	k_{obsd}, sec^{-1}	k_{H_2O}, M^{-1} sec^{-1}
CH_3O	0.000	3.12×10^{-4}	$0.70 \pm 0.10 \times 10^{-4}$
	0.142	3.17×10^{-4}	
	0.258	3.20×10^{-4}	
	0.422	3.38×10^{-4}	
	0.548	3.50×10^{-4}	
	0.698	3.56×10^{-4}	
CH_3	0.000	3.12×10^{-4}	$0.82 \pm 0.12 \times 10^{-4}$
	0.178	3.31×10^{-4}	
	0.275	3.41×10^{-4}	
	0.411	3.55×10^{-4}	
	0.562	3.64×10^{-4}	
	0.684	3.70×10^{-4}	
Cl	0.000	4.29×10^{-4}	$3.11 \pm 0.15 \times 10^{-4}$
	0.217	5.12×10^{-4}	
	0.286	5.31×10^{-4}	
	0.589	6.27×10^{-4}	
	0.710	6.53×10^{-4}	
CF_3	0.230	10.5×10^{-4}	$9.08 \pm 0.93 \times 10^{-4}$
	0.440	12.5×10^{-4}	
	0.628	13.8×10^{-4}	

Rate Dependence on Water Concentration. Isomerization of **1a** in pyridine at 90° containing varying amounts of water produced the values shown in Table IV (see Figure 2). From these data a catalytic rate constant for the contribution of H_2O catalysis to the overall rate is calculated to be $1.82 \pm 0.07 \times 10^{-4}$ in the 1 M mandelaldehyde solution and $1.6 \pm 0.3 \times 10^{-4}$ in the 2 M mandelaldehyde solution. The intercept values for zero H_2O concentration give values of $3.33 \pm 0.03 \times 10^{-4}$ for k_{cat} for mandelaldehyde at 1 M concentration (value from anhydrous pyridine = $3.21 \pm 0.20 \times 10^{-4}$) and $6.5 \pm 0.2 \times 10^{-4}$ for mandelaldehyde at 2 M concentration (value from anhydrous pyridine = $6.42 \pm 0.20 \times 10^{-4}$).

Table VII

Protic species (HA)	[HA], M	k_{obsd}, sec^{-1}	k_a, M^{-1} sec^{-1}
F_3CCH_2OH	0.39	8.63×10^{-4}	$8.1 \pm 0.2 \times 10^{-4}$
	0.80	12.1×10^{-4}	
	1.20	15.1×10^{-4}	
	1.58	18.1×10^{-4}	
	2.00	21.8×10^{-4}	
	2.40	25.6×10^{-4}	
2-Pyridone	0.254	8.75×10^{-4}	$9.6 \pm 0.4 \times 10^{-4}$
	0.490	11.7×10^{-4}	
	0.770	13.6×10^{-4}	
	1.00	15.4×10^{-4}	
	1.26	17.7×10^{-4}	
	1.48	20.6×10^{-4}	
Phenol	0.270	9.78×10^{-4}	$16.1 \pm 0.6 \times 10^{-4}$
	0.490	13.6×10^{-4}	
	0.753	16.4×10^{-4}	
	0.994	21.6×10^{-4}	
	1.20	24.5×10^{-4}	
2-Hydroxymethylpyridine	0.700	9.63×10^{-4}	$4.3 \pm 0.2 \times 10^{-4}$
2-(β-Hydroxyethyl)pyridine	0.700	8.13×10^{-4}	$2.8 \pm 0.2 \times 10^{-4}$
2-(γ-Hydroxypropyl)pyridine	0.700	7.93×10^{-4}	$2.5 \pm 0.2 \times 10^{-4}$
Benzoic acid	0.703	31.8×10^{-4}	$38 \pm 1 \times 10^{-4}$

Deuterium Isotope Measurements. Rate measurements on isomerizations of deuteriomandelaldehyde dimer (**1b**) in anhydrous pyridine at various initial concentrations of **1b** and in aqueous pyridine at various concentrations of water produced the values shown in Table V (see Figure 2). The values shown in Table I were calculated from these data.

Rate Dependence on Para Substituents (Hammett Correlation). Rate measurements in aqueous pyridine at 90° of 1.0 M (calculated as the monomer) solutions of mandelaldehyde substituted in the para position with methoxyl-, methyl-, chloro-, and trifluoromethyl groups gave the results shown in Table VI (see Figures 3 and 4).

Rate Dependence on General Acid Catalyst. Rate measurements of isomerizations of 2.0 M solutions (calculated as the monomer) of mandelaldehyde in pyridine at 90° containing varying amounts of protic species gave the results shown in Table VII (see Figure 5).

Rate Dependence on Benzamidine Concentration. Rate measurements of isomerization of 2.0 M solutions (calculated as the monomer) of mandelaldehyde in pyridine at 90° containing varying amounts of benzamidine, prepared by the method of Beggs and Spencer,[28] gave the results shown in Table VIII.[29]

Table VIII

[Benzamidine], M	k_{obsd}, sec^{-1}
0.000167	8.24×10^{-4}
0.00132	12.4×10^{-4}
0.00252	15.4×10^{-4}
0.00399	21.5×10^{-4}
0.00485	28.0×10^{-4}
0.00858	50.0×10^{-4}

Acknowledgment. This work was supported, in part, by Grant No. 5 RO1 AM 02398 from the National Institutes of Health and Grant No. GP-11087X from the National Science Foundation to whom the authors express their gratitude. We are also indebted to Professor J. L. Kurz for several very helpful discussions during the course of this investigation.

(28) B. H. Beggs and R. D. Spencer, *Anal. Chem.*, 34, 1590 (1962).
(29) We are indebted to Mr. Chung-Lieh Wang for carrying out these measurements.

Organic Photochemistry. XI. The Photocycloaddition of Benzophenone to Conjugated Dienes[1]

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Abstract: The photoreaction of benzophenone with several conjugated dienes leads to oxetanes. Other reaction products are those resulting from transfer of triplet excitation energy from benzophenone to the diene, and hydrogen abstraction by triplet benzophenone. For the benzophenone-2,3-dimethyl-1,3-butadiene reaction, a mechanism of oxetane formation is proposed which involves attack of excited triplet benzophenone on a ground state diene molecule. The rate constant for this cycloaddition is $\sim 1.5 \times 10^6$ M^{-1} sec^{-1} which thus competes inefficiently with the transfer of triplet excitation energy from benzophenone to diene. The further conversion of the photoproducts, under acidic conditions into 1,1-diphenylbutadienes and then into phenylindenes, is described.

Recently there has been considerable interest in the photocycloaddition reactions of carbonyl compounds to olefinic derivatives[2] to yield oxetanes.[3] It was originally proposed that reaction involved attack of the triplet (n,π*) state of the ketone to give the most stable biradical, which subsequently cyclized to the oxetane.[3b] Ketones with lowest (π,π*) triplet states appeared unreactive.[4] However, for aliphatic ketones, it has since been shown that reaction may proceed *via* a complex involving the (n,π*) singlet state of the ketone,[5] or by both singlet and triplet mechanisms si-

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