Kinetics and Mechanism of the Reaction of Phenylglyoxal Hydrate with Sodium Hydroxide to Give Sodium Mandelate[1a]

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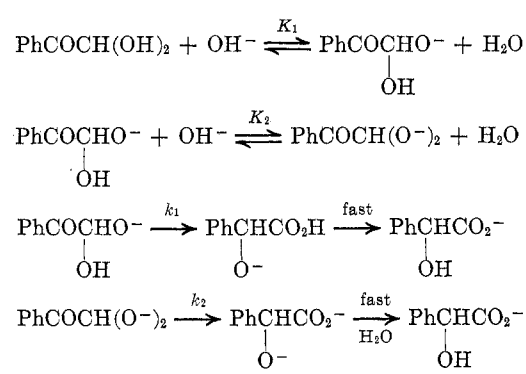
The kinetics of the reaction of phenylglyoxal hydrate with sodium hydroxide to give sodium mandelate in aqueous solution at 35.1° have been studied spectrophotometrically. From the first ionization constant of the aldehyde hydrate, determined by potentiometric titration, and the dependence of the reaction rate on the sodium hydroxide concentration, it is concluded that the reaction proceeds *via* rate-controlling internal hydride ion transfers in the anions $PhCOCH(OH)O^-$ and $PhCOCH(O^-)_2$. Most of the reaction proceeds *via* the double-charged anion at sodium hydroxide concentrations above about 0.003 *M*.

The mechanism of action of glyoxalase, an enzyme that catalyzes the transformation of methylglyoxal to lactate, is of interest in relation to the suggestion that a cancer cell is a cell that has lost its ability to bind its own glyoxalase.[2] For this and other reasons we became interested in the mechanism of the rearrangements of monosubstituted glyoxals to derivatives of α-hydroxy acids, which may be regarded as internal Cannizzaro reactions. Kinetic studies show that in intermolecular Cannizzaro reactions the active hydride ion donor is sometimes the dianion of the aldehyde hydrate **1** and sometimes the monoanion **2**.[3a] According to the concept of "the acidity of transition states,"[3b] the tendency to react *via* the dianion should increase with increasing acidity of the aldehyde hydrate. Since the hydrates of glyoxal derivatives should be more acidic than most aldehyde hydrates, the reaction of a glyoxal derivative with hydroxide ions to give the anion of an α-hydroxy acid might be expected to proceed to a major extent *via* the dianion under conditions where such simple aldehydes as formaldehyde and furfural do. It is not surprising then that the transformation of glyoxal to glycolate by hydroxide ions in aqueous solution is first order in glyoxal and second order in hydroxide ions.[4] It is somewhat surprising, however, that the reaction of phenylglyoxal with hydroxide ion to give mandelate has been reported to be first order in phenylglyoxal and first order in base in 50% aqueous methanol.[5] This difference in behavior cannot be due to a fundamental change in the type of reaction occurring; labeling studies show that it is the hydrogen atom and not the phenyl group that migrates and that this migration is intramolecular[6] just as the corresponding migration of hydrogen in the reaction of glyoxal is.[4,7] In order to compare the phenylglyoxal reaction with Cannizzaro reactions without having to correct for complications arising from solvent effects, we have studied the kinetics of the reaction of phenylglyoxal with sodium hydroxide in water, where several Cannizzaro reactions have been studied.

1 **2**

Results

Crystalline phenylglyoxal hydrate was used in making the reaction solutions. Equilibrium constants for the formation of the dihydrate and each of the two possible monohydrates of phenylglyoxal were calculated from Bell's Taft-equation correlation of the hydration of carbonyl compounds in aqueous solution[8] (using, in some cases, estimated σ^* and E_s values). From the results it was concluded that more than 99% of the material was present as $PhCOCH(OH)_2$ and less than 0.1% as the free aldehyde. The kinetics were followed by uv absorbance measurements at 249.5 nm, where the reactant has an absorption maximum and where the extinction coefficient of the product, sodium mandelate, is less than 2% as large. The sodium hydroxide was present in at least 20-fold excess and linear first-order rate plots were obtained. The rate data were treated in terms of mechanism 1. If the fraction of



(1)

reactant present as the dianion is negligibly small compared with that present as the monoanion and the neutral molecule, and if the concentration of water is absorbed into the equilibrium constants (so that K_1 and K_2 have the dimensions M^{-1}), then the observed first-order rate constants may be expressed as shown

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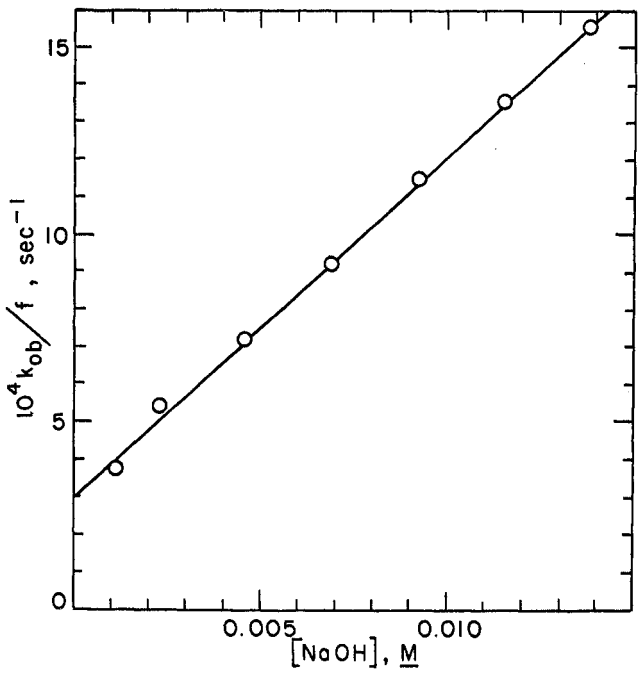

Figure 1.—Plot of k_{obsd} divided by the fraction of phenylglyoxal hydrate present as the monoanion *vs.* the sodium hydroxide concentration.

in eq 2, where f, the fraction of reactant present as the monoanion, may be expressed as in eq 3. The

$$k_{obsd} = f(k_1 + k_2K_2[OH^-]) \quad (2)$$

$$f = \frac{K_1[OH^-]}{1 + K_1[OH^-]} \quad (3)$$

value of K_1 was found to be 247 ± 17 in 0.10 M aqueous sodium chloride at 35° by potentiometric titration. From this result the value of f may be calculated at any given hydroxide ion concentration.

Using the observed first-order rate constants listed in Table I that were determined at ionic strength 0.1 M,

TABLE I
RATE CONSTANTS FOR THE REACTION OF PHENYLGLYOXAL HYDRATE WITH SODIUM HYDROXIDE IN WATER AT 35° [a]

10^3[NaOH], [b] M	A_B [c]	$10^5 k_{obsd}$, sec^{-1}
1.13	0.644	8.01
2.28	0.635	19.5
4.59	0.628	38.1
6.89	0.622	57.8
9.21	0.627	79.5
11.52	0.613	100.2
13.82	0.618	120.1
11.52[d]	0.614	109.0
11.52[e]	0.638	86.6

[a] Initial concentration of phenylglyoxal hydrate about 5.66×10^{-5} M in all runs. Sodium chloride added to bring the ionic strength to 0.10 M except where noted otherwise. [b] This is the average concentration present throughout the run allowing for that used by transformation to mandelate and by partial neutralization of aldehyde hydrate. In the worst case, the initial and final concentrations differ from this by 0.9%. [c] Absorbance extrapolated to zero time. [d] Ionic strength 0.20 M. [e] Ionic strength 0.05 M.

values of k_{obsd}/f were plotted against the hydroxide ion concentration, as shown in Figure 1. According to eq 2, the intercept in this plot, 2.95×10^{-4} sec^{-1}, is equal to k_1, and the slope, 9.14×10^{-2} M^{-1} sec^{-1}, is equal to k_2/K_2.

Comparison of the three runs made in the presence of 0.01152 M sodium hydroxide shows that there is a positive ionic strength effect, as would be expected for a reaction proceeding largely by a mechanism in which a double-charged transition state in the rate-controlling step is formed from two single-charged reactants.

Discussion

The kinetic results obtained are consistent with mechanism 1. An alternative in which the rate-controlling step for that part of the reaction involving two hydroxide ions is the formation, rather than the decomposition, of the dianion would give a kinetic equation with the same form as eq 2. However, calculations of the same type used in a study of the cleavage of phenylpropargylaldehyde[9] show that the formation of the dianion is almost undoubtedly millions of times as fast as that of the mandelate ion.

According to the values of k_1 and k_2K_2 that we have obtained, reaction *via* rearrangement of the dianion is the principal path for reaction at hydroxide ion concentrations above about 0.003 M. There are two important reasons why reaction *via* the dianion should be less important in 50% aqueous methanol, the solvent used by Alexander, than in water. The first is that equilibrium constants for the addition of methanol to carbonyl groups tend to be larger by about 20-fold than the equilibrium constants for addition of water to the same carbonyl groups.[10] Therefore, the reaction solution will contain much more of the methyl hemiacetal of phenylglyoxal, which can rearrange only *via* a monoanion, than of the hydrate, which can rearrange *via* either a monoanion or a dianion. Assuming equal acidities of the hydroxylic hydrogens of the hydrate and the hemiacetal and equal reactivities of the two different monoanions, this factor should increase the relative contribution of reaction *via* the monoanion by about fivefold on going from water to 50% methanol. The second reason for a decrease in the extent of reaction *via* the dianion is the fact that a poorer ion-solvating medium should destabilize a multiply charged transition state relative to a single-charged one. Although there is reason to believe that reaction *via* the dianion should be relatively less important in 50% methanol than in water, it is less clear what the facts are concerning the kinetics of the reaction in 50% methanol. The kinetic equation used was based on the implicit assumption that the fraction of reactant present in a monoanionic form was always negligible.[5] The concentrations of excess base used (as much as 0.03 M) would transform as much as 88% of the phenylglyoxal hydrate present to its conjugate base in aqueous solution. Since the methyl hemiacetal of phenylglyoxal should be about one-half as acidic as the hydrate, and methanol is about one-third as acidic as water, it seems possible that significant fractions of the reactant were present as monoanions in the study in 50% methanol. Ignorance of how much was present in this form makes it difficult to be sure whether any significant fraction of the reaction went through the dianion.

(9) J. Hine and G. F. Koser, *J. Org. Chem.*, **36**, 1348 (1971).
(10) *Cf.* E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968).

Many studies of the kinetics of Cannizzaro reactions have been made.[3a] In a number of these studies the form of the kinetic equation was *assumed*, or the concentrations of reactants were not varied greatly, or the acidity of the aldehyde hydrate was assumed to be negligible, or side reactions (especially prevalent in alcoholic solvents) were neglected, etc. For these reasons a detailed discussion of the factors that influence the relative contributions of reaction *via* the double-charged anion **1** and the single-charged anion **2** is not believed to be worth the space it would require. Hence we shall merely note that the reaction of phenylglyoxal with hydroxide ions is analogous to Cannizzaro reactions in that both the monoanion and dianion may contribute significantly to the reaction.

If the value of K_1 is independent of the ionic strength, as it should be according to the Debye–Hückel limiting law, and if it is the same at 25° as at 35°, then the pK_a of phenylglyoxal hydrate at zero ionic strength is 11.29 at 35° and 11.61 at 25°. According to a Taft-equation correlation of the acidities of aldehyde hydrates at 25°,[9] this is the value it should have if the σ^* constant for the benzoyl group is 1.47. Although Taft lists no value for benzoyl, the value for acetyl (1.65)[11] is not much different from this.

Experimental Section

Reagents.—Various procedures for the purification of phenylglyoxal hydrate gave products with varying melting points perhaps because of the removal of varying amounts of water during the purification. The procedure used for kinetic samples consisted of dissolving the material in ~80% methylene chloride–20% acetone, filtering, and adding hexane. Three such recrystallizations gave colorless needles. The extent of hydration of this material may be somewhat uncertain, but this will have no appreciable effect on the rate constants obtained since the sodium hydroxide was used in large excess.

Kinetic Runs.—In a typical run 3.00 ml of a standard solution of sodium hydroxide and sodium chloride was placed in both the sample and reference cells of a Cary spectrophotometer, Model 14. After thermal equilibrium had been reached at 35.1 ± 0.1°, 12 μl of 1.427×10^{-2} *M* aqueous phenylglyoxal hydrate was added at a recorded time to the sample cell, which was shaken and returned to the cell holder. During the approximately 30 sec that the cell was out of the thermostated cell holder its temperature dropped by about 0.6°, and it then took about 5 min to return to the 35.1 ± 0.1° range. Absorbance measurements at 249.5 nm were recorded from the time the cell was returned to its holder until the reaction was at least 47% and usually about 70% complete. The "infinity" absorbance measured after 10.7 half-lives was found to be 0.012. Rate constants were calculated by the method of least squares from the slope of the plot of log $(A - A_\infty)$ (where A is the absorbance) *vs.* time. The infinity absorbance calculated from the extinction coefficient of sodium mandelate is 0.010. In a duplicate experiment in which the reaction was run at the same concentrations on a 1-l. scale and the solution then evaporated to a smaller volume, the absorption maxima of the mandelate ion at 252, 257, and 263 nm could be seen.[12] The linearity of the plots was about the same as that obtained in the cleavage of phenylpropargylaldehyde.[9]

p*K* Determination.—Recorded potentiometric titrations of 25-ml samples about 0.008 *M* in phenylglyoxal hydrate and 0.100 *M* in sodium chloride were carried out, using a Radiometer automatic titrator (ABU1, PHM26c, SBR2c, and type C electrode), with 2.5 ml of 0.1165 *M* sodium hydroxide at 35.0 ± 0.2°. The total elapsed time was less than 100 sec, during which time less than 1% transformation to mandelate should occur. Analogous titrations were also made on 0.100 *M* sodium chloride reference solutions that contained no phenylglyoxal hydrate. Hydroxide ion concentrations were calculated from eq 4, where $[OH^-]_{ref}$ is

$$[OH^-] = [OH^-]_{ref}\, 10^{pH - pH_{ref}} \quad (4)$$

the hydroxide ion concentration and pH_{ref} the pH at the analogous point of the titration of the reference solution. Values of K_1 were then calculated from eq 5 where $[PhCOCH(OH)_2]_t$ is the total

$$K_1 = \frac{([H^+]/[OH^-]) + ([OH^-]_{ref}/[OH^-]) - 1}{[PhCOCH(OH)_2]_t + [OH^-] - [H^+] - [OH^-]_{ref}} \quad (5)$$

concentration of phenylglyoxal hydrate in all forms. Under the conditions of the titration the two terms containing $[H^+]$ may be neglected. From 11 points taken in each of four titrations the value 247 with a standard deviation of 17 and no clear trend was obtained for K_1.

Registry No.—Phenylglyoxal hydrate, 1075-06-5; sodium hydroxide, 1310-73-2; sodium mandelate, 31657-31-5.

(11) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(12) We are indebted to Mr. Carl D. Fischer, Jr., for carrying out this experiment.