gas-phase reaction in making a quantitative study of substituent effects in aromatic systems free from solvent complications. The discussion in this paper has been limited to elucidating the mechanism of ester pyrolysis. The significance and importance of using gas-phase reactions in quantitatively studying substituent effects, solvent partic-

ipation and the application of gas-phase studies to the current theories of electrophilic aromatic substitution is discussed elsewhere. From a comparison of the *ortho/para* ratios obtained in this and other aromatic reactions of the electrophilic type we propose to evaluate also the steric requirement of the present reaction.

The Mechanism of Decarboxylation of Glycidic Acids[1]

BY V. J. SHINER, JR.,[2] AND BRIAN MARTIN

The decarboxylation of 3-phenyl-2,3-epoxybutanoic acid in "20%" aqueous dioxane has been shown to proceed without appreciable acid or base catalysis in the pH range 4.0–5.5. The reaction has further been shown to involve the production of the enol, 2-phenyl-1-propen-1-ol, as an intermediate. The rate of production of this enol in the decarboxylation reaction and the rate of its ketonization to 2-phenylpropanal have been measured in the pH range 0.5–5.5. Specific acid, water and general base catalysis were detected in the ketonization reaction. The general base catalysis is interpreted as involving general acid attack on the conjugate base of the enol. This is the reverse of the accepted mechanism for base-catalyzed enolization.

Introduction

The Darzens glycidic ester condensation followed by hydrolysis to the glycidic acid and decarboxylation is a well-known synthetic route for the preparation of aliphatic aldehydes.[3] The condensation reaction has been studied and its mechanism reasonably well characterized.[4] The conversion of glycidic esters to glycidic acid salts is generally effected by simple aqueous alkaline hydrolysis. Glycidic acids produced by acidification of aqueous solutions of the salts are generally decarboxylated directly without purification either by warming the aqueous solution[5] or separating the acid and heating.[6,7]

However, in a few reported examples,[6b,7] the glycidic acids themselves have been isolated, purified by recrystallization and characterized, although they are apparently not particularly stable at room temperature and decarboxylate readily on heating. Dullaghan and Nord[8] report that some α-alkylglycidic acids decarboxylate more readily than similar ones not having α-alkyl substituents. These authors also report that acidification of the glycidic acid salts with acetic acid gives better yields of carbonyl (decarboxylation) products than acidification with phosphoric or hydrochloric acid or pyrolysis of the sodium salts.

Little, if any, further information relevant to the mechanism of the decarboxylation reaction is available, although Arnold[9] has suggested a cyclic
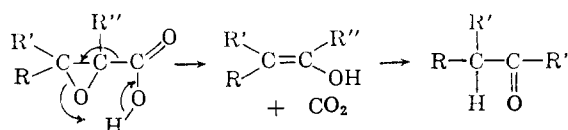

process producing the enol of the product as an intermediate.

Enol intermediates have been shown to be produced in the decarboxylation of β-keto acids and dimethyloxaloacetic acid.[10]

Results and Discussion

In the course of another investigation it was desired to prepare 2-phenylpropanal and 2-phenyl-propanal-2-*d*. It was found that decarboxylation of 3-phenyl-2,3-epoxybutanoic acid in deuterium oxide gave the 2-deuterio compound. This result
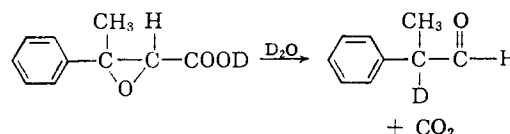
is inconsistent with an *a priori* less likely mechanism involving the formation of the α-keto acid by epoxide ring opening and rearrangement followed by decarboxylation. Some α,β,β-trialkyl substituted glycidic acids were originally thought to decarboxylate to aldehydes, which would require an α–β shift of the alkyl group. These rearrangements have subsequently been shown not to take place in the manner originally suggested; the products are in all cases ketones and the α-alkyl group does not migrate.[6] Thus all known glycidic acid decarboxylations seem to involve fundamentally the same structural alterations; carbon dioxide is lost, the epoxide ring opens and the new C–H bond is formed at the position α to the carbonyl group in the product.

(1) Presented in part before the Division of Organic Chemistry, American Chemical Society, Atlantic City, N. J., September, 1962.

(2) Alfred P. Sloan Research Fellow.

(3) M. S. Newman and B. J. Magerlein, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 413–440.

(4) M. Balaster, Chem. Revs., 55, 283 (1955).

(5) C. F. H. Allen and J. VanAllan in E. C. Horning, ed., "Organic Syntheses," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 733.

(6) (a) H. H. Morris and C. J. St. Lawrence, J. Am. Chem. Soc., 77, 1692 (1955). (b) H. H. Morris and R. H. Young, Jr., ibid., 77, 6678 (1955).

(7) F. F. Blicke and J. A. Faust, ibid., 76, 3156 (1954).

(8) M. E. Dullaghan and F. F. Nord, J. Org. Chem., 18, 878 (1953).

(9) R. T. Arnold, Abstracts of Papers Delivered at the Tenth National Organic Symposium of the American Chemical Society, Boston, Mass., 1947.

(10) (a) See J. Hine, "Physical Organic Chemistry," 2nd Edition, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 303–306, for a summary of the information and references to the original literature. (b) R. Steinberger and F. H. Westheimer, J. Am. Chem. Soc., 73, 429 (1951).

Since solutions of the glycidic acid salts do not decarboxylate readily it appeared that either the glycidic acids decompose directly or are subject to acid-catalyzed decomposition. In order to determine the presence or absence of additional acid catalysis it was decided to measure the decarboxylation rate at several pH's. Since the product aldehyde showed greater absorption at 2600 Å. than the glycidic acid, it appeared that the conversion could be followed by measuring the increase in absorption at that wave length. However, it was found that the reaction solution actually showed an exceptionally large increase in optical density followed by an exponential decrease to a constant value. This behavior is characteristic of a reaction involving the formation and disappearance of a metastable intermediate which has a greater optical density at the measured wave length than either the starting material or product. Since the disappearance of the intermediate was relatively slow it was possible to record its ultraviolet spectrum. This showed a λ_{max} at 2580 Å. and was essentially identical to the spectrum shown by a solution prepared by dissolving 2-phenylpropanal in dilute sodium hydroxide and adding this to a sodium citrate buffer of the same composition as that used in the decarboxylation reaction. Furthermore, the rate of disappearance of optical density at 2600 Å. was the same for both solutions; $k_1 = 1.48 \times 10^{-3}$ sec.$^{-1}$ for the first solution and 1.52×10^{-3} sec.$^{-1}$ for the second, both at pH 4.05 and 25°. It thus appears that the enol, 2-phenyl-1-propen-1-ol, is an intermediate in the decarboxylation reaction as suggested by Arnold.[9] The mechanism is thus closely analogous to that believed to obtain in β-keto acid decarboxylations.[10]

The enol function seems to require remarkably little in the way of stabilizing structural features to make it ketonize sufficiently slowly to be readily detected in aqueous solution. Steinberger and Westheimer observed the ultraviolet spectrum of the enol form of α-ketoisovaleric acid produced in the decarboxylation of dimethyloxaloacetic acid.[10b] Fuson, Corse and McKeever isolated a stable enol, 1,2-dimesityl-1-propen-1-ol.[11] The presently reported example is probably the simplest enol which has been observed directly by standard techniques. It is not stabilized by an adjacent oxygen function which allows hydrogen bonding and it has only one β-phenyl group for conjugation stabilization.

The complete reaction thus consists of two successive stages; first, loss of carbon dioxide to give the enol, followed by prototropy of the enol to the aldehyde. The rate constants for decarboxylation of the acid in solutions buffered with sodium citrate have been determined from the following relationship for two consecutive first-order reactions[12]

$$t_{max} = (2.303 \log k_1'/k_1'')/(k_1' - k_1'')$$

where t_{max} is the time at which the maximum concentration of the intermediate enol occurs; k_1' is the first-order rate constant of the first of the

(11) R. C. Fuson, J. Corse and C. H. McKeever, *J. Am. Chem. Soc.*, **62**, 3250 (1940).

(12) S. Glasstone, "Textbook of Physical Chemistry," 2nd Edition, D. Van Nostrand, New York, N. Y., 1946, p. 1077.
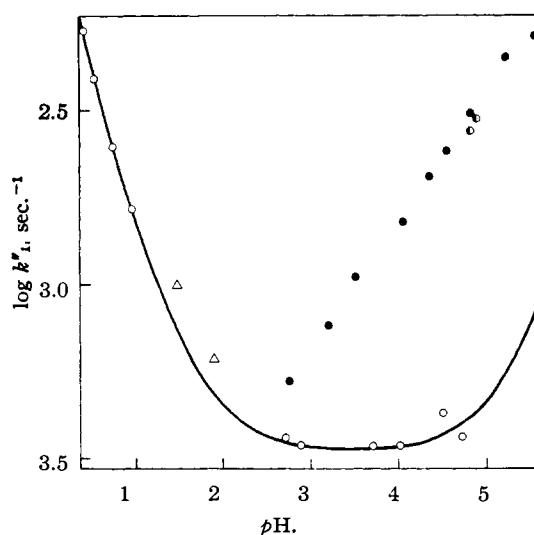
Fig. 1.—Ketonization rate constants vs. pH: O, rate constants in non-buffered solutions; △, in presence of 0.1 M KCl; ●, in sodium citrate buffer; ◐, in sodium acetate buffer.

reactions, the decarboxylation of the acid; and k_1'' is the first-order rate constant of the second of the reactions, the ketonization of the enol. The latter was measured independently in the same buffer solutions by generating the enol from 2-phenylpropanal in sodium hydroxide solution as described above. The apparent decarboxylation rate constant, k_1', varies with pH because the proportion of the reactant present as acid or anion changes with changing pH. If one assumes that only the acid form decarboxylates at an appreciable rate, the first-order rate constants for this reaction, k_{GH}, can be obtained by dividing the apparent rate constants, k_1', by the fraction of the reactant present in the acid form at each pH

$$[GH]/([GH] + [G^-]) = [H^+]/(k_A + [H^+])$$

where k_A is the acid dissociation constant, 6.46×10^{-4} mole/liter, of 3-phenyl-2,3-epoxybutanoic acid, GH; the anion of the acid is G^- and brackets refer to concentrations. The k_{GH} values shown in Table I are constant within experimental error, over the pH range studied, indicating that only the acid species decarboxylates at an appreciable rate under these conditions. The reaction is thus a simple decomposition of the free epoxy acid, or, as is indistinguishable from it kinetically, an acid-catalyzed decomposition of the anion of the acid
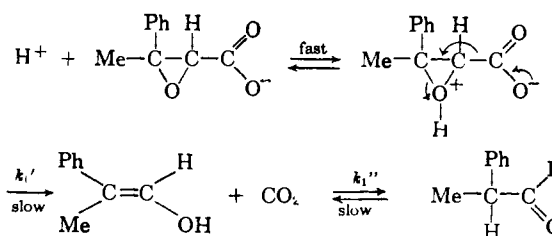
The distinction between this mechanism, involving the zwitterionic intermediate, and the one proposed by Arnold with a cyclic transition state is probably more semantic than real. The same

problem has been discussed fairly extensively for the decarboxylation of β-keto acids.[10a]

TABLE I

RATE CONSTANTS FOR THE DECARBOXYLATION OF SODIUM 3-PHENYL-2,3-EPOXYBUTANOATE IN SODIUM CITRATE BUFFER SOLUTIONS

pH	4.05	4.35	4.54	4.81	5.23
k_1'', 10^{-3} sec.$^{-1a}$	1.52	2.05	2.38	3.07	4.50
t_{max}, sec.^{b}	425	508	575	635	715
k_1', 10^{-3} sec.$^{-1c}$	3.47	1.88	1.23	0.672	0.210
[GH]/([GH] + [G$^-$])^d	0.1213	0.0646	0.0426	0.0231	0.00904
k_{GH}, 10^{-3} sec.$^{-1e}$	2.86	2.91	2.89	2.91	2.32

ᵃ Constant for ketonization of 2-phenyl-1-propen-1-ol. ᵇ Time for maximum concentration of 2-phenyl-1-propen-1-ol in the decarboxylation reaction. ᶜ Apparent first-order rate constant for decarboxylation. ᵈ Fraction of total reactant present as glycidic acid. ᵉ First-order rate constants for decarboxylation of the acid form.

The rates of ketonization of the intermediate enol have been measured in non-buffered hydrogen chloride solutions in aqueous dioxane over the pH range 0.5–5.5, the enol being generated from sodium 3-phenyl-2,3-epoxybutanoate. The logarithms of the first-order rate constants, shown plotted against pH in the figure, reach a minimum value and increase steadily as the acid concentration increases or decreases from that at the minimum. This indicates the simultaneous operation of acid, base and solvent-catalyzed reactions. If this is the case, the relationship between first-order rate constant k_1'', hydrogen ion and hydroxide ion concentrations is of the form[13]

$$k_1'' = k_{H_2O} + k_{H^+}[H^+] + k_{OH^-}[OH^-]$$

Then it can easily be shown that the log k_1'' versus pH plot is symmetrical about the minimum and approaches unit slope at high and low acid concentrations. The best curve of this nature which satisfies the observed data is described by: $k_{H_2O} = 3.3 \pm 0.1 \times 10^{-4}$ sec.$^{-1}$, $k_{H^+} = 1.2 \pm 0.1 \times 10^{-2}$ liter-mole^{-1}-sec.$^{-1}$, $k_{OH^-} = 1.35 \pm 0.1 \times 10^5$ liter-mole^{-1}-sec.$^{-1}$. These values give a minimum first-order ketonization rate constant of 3.37×10^{-4} sec.$^{-1}$ at pH 3.48. The curve to this equation is drawn on the figure.

The ketonization reactions in sodium citrate buffer solutions (0.1 g. ion/liter of total citrate), listed in Tables I and II and plotted on the figure, are considerably faster than those in unbuffered solutions of the same pH. The fact that this discrepancy is small at pH 2.7 and increases markedly toward pH 5 indicates that this is predominantly general base catalysis by the citrate ions rather than general acid catalysis. This general base catalysis may be correlated with the calculated concentrations of the three citrate bases (H$_2$Cit$^-$, HCit$^=$ and Cit$^≡$) in the buffer solutions. The following catalytic coefficients give the best fit to the data: $k_{H_2Cit^-} = 7.2 \times 10^{-3}$ liter-mol^{-1}-sec.$^{-1}$, $k_{HCit^=} = 3.8 \times 10^{-2}$ liter-mole^{-1}-sec.$^{-1}$, $k_{Cit^≡} = 5.0 \times 10^{-2}$ liter-mole^{-1}-sec.$^{-1}$. That this fit is satisfactory is shown by the comparison of calculated and observed over-all first-order rate constants for ketonization in citrate buffers of various pH's given in Table II.

(13) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, pp. 6-9.

The calculated values were obtained using the expected rates in unbuffered solution, the above catalytic coefficients, and the calculated concentrations of the respective species. Similarly, the acetate ion catalytic coefficient was calculated from the three runs made in 0.1 M sodium acetate-acetic acid buffer solution to be 4.51×10^{-2} liter-mole^{-1}-sec.$^{-1}$. All of these catalytic coefficients are only approximate because the calculations neglect salt effects and activity coefficients.

TABLE II

KETONIZATION RATE CONSTANTS IN SODIUM CITRATE BUFFER SOLUTIONS

| pH	2.75	3.21	3.51	4.05	4.35
k_1 (obsd.)^a	0.52	0.75	1.05	1.52	2.05
k_1 (calcd.)^{a,b}	0.60	0.82	0.99	1.51	2.00
pH	4.54	4.815	5.23	5.56	
k_1 (obsd.)^a	2.38	3.07	4.50	5.10	
k_1 (calcd.)^{a,b}	2.40	3.12	4.29	5.10	

ᵃ Units are 10^{-3} sec.$^{-1}$. ᵇ Calculated using the catalytic coefficients given in the text for H$_2$O, OH$^-$, H$_3$O$^+$, the citrate ions and the calculated concentrations of these species.

From these data, and by analogy with the reverse reaction, the enolization of ketones, which is well understood, the mechanism of the ketonization may be expressed as

acid catalysis
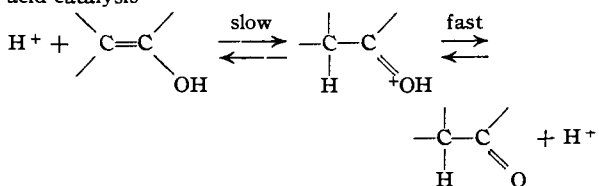
base catalysis
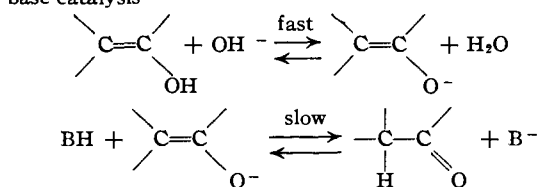
Alternatively, both of these reactions may involve only one step, through concerted attack by acid on carbon-2 and base on the oxygen-bound proton.[14] The present data do not serve to distinguish between these possibilities.

The base-catalyzed reaction most likely involves specific hydroxide ion catalysis in the first step and general acid catalysis in the second. Therefore, the reactions in buffered solutions, for which the rate equations involve the concentration of the anion, are represented in the mechanism as catalyzed by hydroxide ion in the first step and the conjugate acid of the anion in the second. The solvent-catalyzed component of the rate may similarly be represented in this scheme, with hydronium ion acting as the acid in the second step. The rate equation may then be better represented by replacing the terms in concentration of the anion [B$^-$] with K_A[OH$^-$][HB]/K_W, where K_A is the dissociation constant of the acid HB and

(14) C. G. Swain, A. J. DiMilo and J. P. Cordner, J. Am. Chem. Soc., 80, 5983 (1958).

K_W the ion product constant of water

$$k_1'' = \{3.28 \times 10^{10}[OH^-][H_3O^+] + 1.22 \times 10^{-2}[H_3O^+] + 2.43 \times 10^3[OH^-][H_2O] + 6.24 \times 10^5[OH^-][H_3Cit] + 6.90 \times 10^7[OH^-][H_2Cit^-] + 2.00 \times 10^7[OH^-][HCit^-] + 7.92 \times 10^7[OH^-][HAc]\} \text{ sec.}^{-1}$$

These general acid catalytic coefficients show a reasonably good Brönsted correlation with the acid dissociation constants,[15] the coefficient α being about 0.4. The correlation must be considered only approximate because salt effects have been ignored, considerable weight given to the points for H_2O and H_3O^+ and no statistical corrections were made for the citrate species.

Experimental

Sodium 3-phenyl-2,3-epoxybutanoate was prepared by Darzen's method[5] and recrystallized from ethanol–water to a constant melting point of 258°.

2-Phenylpropanal.—A solution of 307 g. (1.53 moles) of sodium 3-phenyl-2,3-epoxybutanoate in 1 l. of water was stirred at room temperature as 200 ml. of concentrated hydrochloric acid (2.0 moles) was added dropwise. It was then boiled under reflux for an hour. The product was extracted with ether, washed, dried, and fractionated at reduced pressure through an 18 × 400 mm. Nestor spinning band column; b.p. 71° (5.0 mm.), yield 155 g., 75%.

Dioxane was technical grade which had been fractionally distilled from excess sodium through a vacuum jacketed 13 × 870 mm. column packed with steel helices; b.p. 101°. 20% Dioxane–80% water by volume was made up by weight from distilled water which had been passed through an Amberlite MBI ion exchange column.

Decarboxylation in Deuterium Oxide.—A sample of 5 g. (0.025 mole) of sodium 3-phenyl-2,3-epoxybutanoate was refluxed for 1 hour in acidic 97% deuterium oxide solution prepared by dissolving 0.030 mole of dry hydrogen chloride in 10 ml. of deuterium oxide. The product was extracted with ether, washed rapidly with water and fractionally distilled under reduced pressure through an 18 × 400 mm. Nestor spinning band column; b.p. 66° (4.0 mm.).

N.m.r. Spectra and Deuterium Analysis.—The position and extent of deuterium substitution in the product obtained from decarboxylation in deuterium oxide was determined by analysis of its proton magnetic resonance spectrum observed using a Varian DP-60 magnetic resonance spectrometer. Spectra were run at 60 mc. in carbon tetrachloride solutions with tetramethylsilane as the internal reference standard. 2-Phenylpropanal showed three groups of lines characteristic of the three types of aliphatic protons: (1) a partly resolved doublet centered at 9.62δ, $J = \sim 1$ c.p.s., characteristic of the aldehyde hydrogen; (2) a quartet centered on 3.53δ, $J = 7$ c.p.s., characteristic of the α-hydrogen; (3) a doublet centered at 1.40δ, $J = 7$ c.p.s., characteristic of the methyl group. The deuteration product showed strongly reduced absorption at 3.53δ and an absence of the splitting (characteristic of the hydrogen compound) at 9.62 and 1.40δ. Comparison of the relative heights of the bands near 3.53 δ with those of the phenyl proton absorption near 7.18δ in the two samples indicated a hydrogen content in the α-position of 2-phenylpropan-2-d-al of 0.15 to 0.25 atom per molecule. This was slightly higher than expected and probably resulted from some exchange of the deuterium at the α-position with water in the washing or purification steps.

Ultraviolet spectra were taken on a Cary model 14 recording spectrophotometer. Sodium 3-phenyl-2,3-epoxybutanoate showed a λ_{max} at 2595 Å. with ϵ_{max} equal to 185. 2-Phenylpropanal showed a λ_{max} of 2460 Å. and ϵ_{max} of 850. 2-Phenyl-1-propen-1-ol showed a λ_{max} at

(15) Reference 13, Ch. 5.

2580. The ϵ_{max} for this compound, 11,400, was calculated from its maximum concentration during a kinetic run, C_{max}, obtained from the following relationship for consecutive reactions[12]

$$C_{max}/a = (k_1''/k_1')^{k_1''/k_1' - k_1''}$$

where a is the initial concentration of starting material.

Kinetics.—To start a run, a volume of sodium 3-phenyl-2,3-epoxybutanoate in dioxane–water was added with a hypodermic syringe to sodium citrate buffer solution thermostated at 25 ± 0.05°, such that the concentration of the reacting species was 2×10^{-4} M. The cell in the block of the spectrophotometer was filled immediately with this solution, and the increasing optical density at 2600 Å. was recorded, the time from the moment of mixing to the maximum optical density being measured. The rate constant for the decarboxylation was calculated from this and the rate constant of the second of the reactions, the ketonization of the enol, measured as follows.

2-Phenylpropanal (6.5 mg.) was dissolved in 5 ml. of "20%" dioxane–water 0.1 N in sodium hydroxide. Immediately 0.5 ml. of this solution was added to 25 ml. of the same buffer solution as used for the decarboxylation, giving a 2×10^{-4} M solution of total enol and aldehyde. The spectrophotometer cell was filled with this solution and from the decreasing optical density, showing good first-order kinetics for over 90% reaction, the first-order rate constant of the ketonization of the enol was calculated.

Three runs were also made in this manner in 0.1 M sodium acetate–acetic acid buffer solution (Table III).

TABLE III

RATE CONSTANTS OF THE KETONIZATION OF 2-PHENYL-1-PROPEN-1-OL IN SODIUM ACETATE–ACETIC ACID BUFFER SOLUTION

pH	k_1^{obsd} $\times 10^3$	$k_1^{calcd a}$ $\times 10^4$	[CH$_3$COO$^-$]	$(k_1^{obsd} - k_1^{calcd})/$ [CH$_3$COO$^-$]	
4.81	2.73	4.16	0.0532	4.37×10^{-2}	Average
4.87	3.05	4.28	.0566	4.62×10^{-2}	4.52 ×
4.88	3.03	4.33	.0570	4.56×10^{-2}	10^{-2}

a Calculated for reaction at the given pH in the absence of general catalysis.

At pH 4.05 the rate of ketonization was also measured by recording the decreasing optical density after the maximum had been reached during the decarboxylation. One half-life after the maximum enol concentration, $\log (D - D_\infty)$ was plotted against time for a further four half-lives. This plot was linear over the latter two-thirds of its length to give a first order rate constant of 1.48×10^{-3} sec.$^{-1}$.

In non-buffered solutions the rate of ketonization of the enol could be measured by this latter method only at acid concentrations greater than pH 2. At higher pH values the enol was generated by dissolving sodium 3-phenyl-2,3-epoxybutanoate (20 mg.) in 5 ml. of dioxane–water and acidifying to $ca.$ pH 2 by adding 0.15 ml. of 1.0 N hydrochloric acid. After 30 minutes, approximately one half-life after the maximum concentration of enol, 0.5 ml. of this solution was added to 50 ml. of dioxane–water at 25° to which varying small concentrations of sodium hydroxide solution had been added, and the rate of ketonization in this solution was measured.

Measurements of pH were made with a Leeds and Northrup model 7664 pH meter at 25°. For pH values less than one, the reaction mixtures were titrated directly against sodium carbonate.

The dissociation constant of 3-phenyl-2,3-epoxybutanoic acid was estimated, by rapid titration of the sodium salt with hydrochloric acid at 5°, to be 6.46×10^{-4} mole/liter.