The Acid-Catalyzed Reactions of
β-Hydroxy-β-phenylbutyric Acid[1]

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In 50% sulfuric acid, the rates of dehydration of β-hydroxy-β-phenylbutyric acid (I) to 3-phenyl-3-butenoic acid (III) and to 3-phenyl-2-butenoic acid (β-methylcinnamic acid) (II) are nearly the same. Competitive decarboxylation of I occurs under these conditions as well. The rates of hydration of II and III have also been studied. The implications of this complex network of reactions are discussed.

Introduction

In recent years several studies of the mechanism of acid-catalyzed dehydration have been reported from these laboratories, involving a variety of compounds, including β-hydroxy ketones[2-4] and β-hydroxy-β-arylpropionic acids[5,6] and 1,2-diarylethanols.[7]

These studies have shown that more than one mechanism may be operative, depending upon the structural environment and the nature of the functional groups near the hydroxyl group. With but one exception[4] these studies have been carried out on secondary alcohols. It is the purpose of the present report to discuss the behavior of a closely related tertiary alcohol, β-hydroxy-β-phenylbutyric acid (I).

Previous investigations of the reactions of such tertiary alcohols have been carried out in many different contexts, but with little consideration of kinetic data.

As will be clear from the results here, this particular system shows a fairly complex network of reactions, with similar rates. However, when these complexities are unravelled, the results and derived conclusions add considerably to one's understanding of these systems.

Arbuzow[8] observed that I reacts on dissolution in concentrated sulfuric acid to give β-methylcinnamic acid, II, while dry distillation of the analogous β-(2,4-dimethylphenyl)-β-hydroxybutyric acid was reported by Mazurewitsch[9] to give 2-(2,4-dimethylphenyl)propene. Similarly the result of boiling α-ethyl-β-hydroxy-β-phenylpropionic acid with dilute sulfuric acid is the formation of 1-phenyl-1-butene.[10] These two modes of reaction are further complicated when one

considers also the possibility of concomitant formation of 3-phenyl-3-butenoic acid (III) from I. The formation of a mixture of α,β-unsaturated and β,γ-unsaturated isomers is best documented in the reactions of the esters of compounds related to I.

Treatment of ethyl β-hydroxy-β-phenylbutyrate with phosphorus oxychloride gives a mixture of unsaturated esters from which Johnson and Kon[11] isolated a small proportion of the β,γ-unsaturated acid III. Recently Benkeser, Hooz, Liston, and Trevillyan[12] have shown that the mixture of esters contains 69% of the methyl ester of II, 25% of the methyl ester of III, and 6% of methyl *cis*-β-methylcinnamate. Johnson and Kon found that, upon treatment with concentrated alkalies, III was converted almost completely to β-methylcinnamic acid. They also investigated the behavior of higher homologs. β-Ethylcinnamic acid is substantially converted to its β,γ isomer by alkali. Boiling with 50% sulfuric acid produces a similar result along with the formation of α-ethylstyrene. Cologne and Chambion[13] report that iodine-catalyzed dehydration of ethyl β-hydroxy-β-(p-tolyl)butyrate gives 90% of the α,β-unsaturated isomer and 10% of the β,γ-unsaturated ester.

Experimental

β-Hydroxy-β-phenylbutyric Acid. A solution of 2.32 g. of ethyl β-hydroxy-β-phenylbutyrate (prepared by the Reformatsky reaction[14] of ethyl bromoacetate with acetophenone in 85% yield, b.p. 98–100° (1.1 mm.)) in 80 ml. of methanol was added to 10 ml. of 1.0 N KOH and allowed to stand overnight at room temperature. Removal of methanol under reduced pressure afforded an oily residue which was dissolved in water and titrated with dilute HCl. The cloudy suspension was extracted with ether and the ether extracts were dried over MgSO₄ and concentrated. The residue slowly crystallized. Recrystallization was attended with some difficulty. From benzene–cyclohexane, crystals of m.p. 45–49° were obtained (lit.[9] m.p. 50–53°) of satisfactory analysis. Sublimation afforded a mixture of two different crystalline forms which could be mechanically separated, one, m.p. 52–56°, the other, m.p. 68–69.5°. Very slow sublimation to a cold finger previously seeded with the higher melting polymorph afforded a satisfactory method for processing the material, m.p. 70–72°. The infrared spectra (CHCl₃) and ultraviolet spectra (ethanol) of the two different crystalline modifications are essentially identical. On long standing, the lower melting form changes to the higher melting one.

(1) Supported in part by grants from the National Science Foundation NSF-G-13125 and NSF-GP-1572.
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(4) D. S. Noyce and M. J. Jorgenson, *J. Org. Chem.*, **28**, 3208 (1963).
(5) D. S. Noyce and C. A. Lane, *J. Am. Chem. Soc.*, **84**, 1635, 1641 (1962).
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(10) Andres, *J. Russ. Phys. Chem. Soc.*, **28**, 289 (1896); F. K. Beilstein, "Handbuch der organischen Chemie," Vol. X, 4th Ed., 1919, p. 276.

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(12) R. A. Benkeser, J. Hooz, T. V. Liston, and A. E. Trevillyan, *J. Am. Chem. Soc.*, **85**, 3984 (1963).
(13) J. Cologne and J. Chambion, *Bull. soc. chim. France*, [5] **15**, 999 (1947).
(14) R. L. Shriner, *Org. Reactions*, **1**, 17 (1947).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.66; H, 6.71; neut. equiv., 180. Found: C, 66.88, 66.45; H, 6.62, 6.82; neut. equiv., 179.6, 181.6.

trans-β-Methylcinnamic Acid. Five grams of β-hydroxy-β-phenylbutyric acid was dissolved in a small amount of ethanol and poured into 100 ml. of 70% sulfuric acid. The sulfuric acid solution was immediately extracted with four 25-ml. portions of benzene. The combined benzene extracts were washed with water, dried, and concentrated. *trans-β*-Methylcinnamic acid crystallized in 50% yield; recrystallized from carbon disulfide, m.p. 98–99° (lit.[15] m.p. 98–99°).

cis-β-Methylcinnamic acid was prepared by ultraviolet irradiation of *trans-β*-methylcinnamic acid and crystallization from carbon disulfide, m.p. 133–133.5° (lit.[16,17] m.p. 129, 131.5°).

3-Phenyl-3-butenoic Acid. From α-methylstyrene, 3-bromo-2-phenyl-1-propene was prepared by the method of Hatch and Patton.[18] Following the procedure of Young, Prater, and Winstein,[19a] the Grignard reagent of 3-bromo-2-phenyl-1-propene was prepared. To 15 g. of magnesium turnings and 100 ml. of ether in a 500-ml. three-necked flask equipped with a dropping funnel, a condenser, and a strong stirrer, a solution of 25 g. of 3-bromo-2-phenyl-1-propene in 100 ml. of dry ether was added slowly (3 hr.) with very vigorous stirring. When addition was complete, the greenish colored Grignard solution was poured over 50 g. of crushed Dry Ice. Saturated ammonium chloride solution was added, and the mixture was worked up in the usual manner, taking precautions to keep the solutions cold, and the acidic solutions dilute. The dried ether extracts were concentrated to afford a solid interspersed in an oil. Washing the solid with petroleum ether (b.p. 30–60°) to preferentially remove the β,γ isomer, 3-phenyl-3-butenoic acid, as reported by Johnson and Kon,[12] afforded a petroleum ether solution of material which was largely III. Evaporation of the ether left a clear oil (satisfactory analysis and neutral equivalent) which was examined by ultraviolet and n.m.r. spectra.[19b] From the spectra it was determined that the composition of the oil was 62% III, 22% II, and 16% *cis-β*-methylcinnamic acid.

Kinetic Methods. A. Rates of hydration and of dehydration were followed spectrophotometrically as previously described[20] using a Beckman D.U. spectrophotometer with a thermostated cell block. A Cary Model 14 recording spectrophotometer was used to record complete ultraviolet spectra.

B. Decarboxylation was followed by volumetric methods. Alternatively some studies of decarboxylation were carried out by observing the loss of absorbance due to β-methylcinnamic acid.

C. A typical run, using initial rate techniques, is tabulated in Table I.

(15) H. Rube, *Ann.*, **369**, 323 (1909).
(16) M. Tiffeneau, *Compt. rend.*, **138**, 985 (1904).
(17) R. Stoermer, F. Grimm, and E. Laage, *Ber.*, **50**, 959 (1917).
(18) L. F. Hatch and T. L. Patton, *J. Am. Chem. Soc.*, **76**, 2705 (1954).
(19) (a) W. G. Young, A. N. Prater, and S. Winstein, *ibid.*, **55**, 4909 (1933); (b) our spectra are in complete accord with the n.m.r. spectra reported for the corresponding methyl esters; ref. 12.
(20) D. S. Noyce and M. J. Jorgenson, *J. Am. Chem. Soc.*, **83**, 2525 (1961).

Table I. Initial Rate of Dehydration of β-Hydroxy-β-phenylbutyric Acid[a]

Time, sec.	A_{243}	A_{273}	[II] × 10⁵, moles/l.[b]	[III] × 10⁵, moles/l.[c]
240	0.216	0.215	1.44	1.33
300	0.237	0.244	1.64	1.43
360	0.258	0.273	1.83	1.52
420	0.278	0.301	2.02	1.61
480	0.297	0.327	2.19	1.70
540	0.314	0.353	2.37	1.77
600	0.330	0.377	2.53	1.84
660	0.345	0.401	2.69	1.90
720	0.360	0.424	2.85	1.96

[a] H_2SO_4 = 49.3%; at 25.00°; $[I]_0$ = 3.55 × 10⁻⁴ mole/l. [b] [II] = $A_{273}/14,900$. [c] [III] = $(A_{243} - 5700[II])/10,100$.

Results

Our results are accommodated by the following reaction scheme.
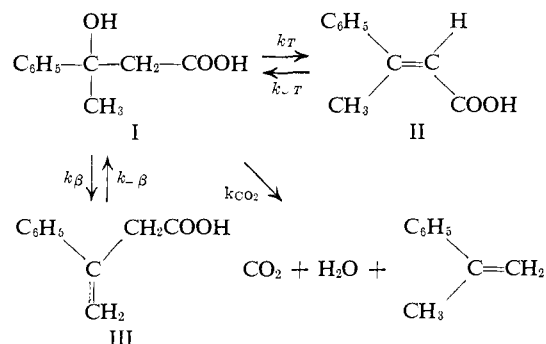
A solution of I in 50% sulfuric acid evolves 30% of the theoretical amount of CO_2 in 5 hr. at room temperature; after this time there is a fairly distinct change in the rate of evolution of CO_2. More slowly, the remaining 70% of the theoretical amount of CO_2 is evolved. Concomitantly, the absorbance at 273 mμ rises and reaches a maximum after 5 hr., and then slowly decreases. Thus there appears to be established a pseudo-equilibrium among two or more species after about 5 hr. The intensity of absorption (at 273 mμ) corresponds to the conversion of 45% of the original hydroxy acid to β-methylcinnamic acid at this time. The remainder of the material can be accounted for as 3-phenyl-3-butenoic acid (β-methylenehydrocinnamic acid) (III) and hydroxy acid (I) in addition to the products resulting from the 30% of α-methylstyrene which has been formed during this time. In 50% sulfuric acid α-methylstyrene is immediately and almost completely hydrated,[21,22] and therefore contributes essentially no absorption in the regions under study. Presumption that the *cis* isomer of β-methylcinnamic acid represents most of the "missing" 25% of material is inconsistent with the experimental observations.

Making measurements of the changes in absorbance *vs.* time at 243 mμ (where III is the most intensely absorbing species) in conjunction with the absorbance at 273 mμ allows the calculation of the total composition after 300 min. as: II, 44%; III, 4%; I, 22%; and CO_2, 30%. Thus, the rates of formation of II, of III, and the rate of decomposition of I to give

(21) H. J. Peterson, Ph.D. Dissertation, Pennsylvania State University; *Dissertation Abstr.*, **21**, 2489 (1961).
(22) W. M. Schubert, B. Lamm, and J. R. Keeffe, *J. Am. Chem. Soc.*, **86**, 4727 (1964).

CO$_2$, H$_2$O, and α-methylstyrene are comparable under these experimental conditions. The amount of I remaining at this time represents a pseudo-equilibrium concentration of I with II and III.

Further careful consideration of these results as affected by changes in the mineral acid concentration allows development of correlation patterns by which extrapolations may be made to other compounds and to other conditions. We shall discuss each of these processes in turn.

Discussion

The Equilibrium between I and III. From the initial rate of hydration of III in 50% sulfuric acid, and from the initial rate of dehydration of I to form III, it is possible to calculate the equilibrium constant for the interconversion of I and III, isolated from the other reactions occurring simultaneously in this system.

From the data in Table II, in conjunction with the initial rate of formation of III from I (Table III), it can be seen that the alcohol predominates at equilibrium. The equilibrium constant in 39% sulfuric acid, K = [I]/[III] = 9.1, is more properly calculated by inclusion of the activity of water; the equilibrium constant at unit water activity, calculated from the relative rates of hydration and dehydration in 39% sulfuric acid, is 16.

Table II. Hydration of 3-Phenyl-3-butenoic Acid at 25.00°

H$_2$SO$_4$, %	$-H_0$	$k_{-\beta}$ sec.$^{-1}$	a_{H_2O}	log $k + H_0$
38.86	−2.33	6.63 × 10^{-5}	0.589	−6.51
44.40	−2.79	17.2 × 10^{-5}	0.471	−6.55
49.15	−3.30	48.6 × 10^{-5}	0.369	−6.61

Table III. Initial Rate of Formation of III from I at 25.00°

H$_2$SO$_4$, %	$-H_0$	k_β, sec.$^{-1}$	log $k + H_0$
38.90	−2.33	0.73 × 10^{-5}	−7.47
45.13	−2.86	2.45 × 10^{-5}	−7.47
49.28	−3.31	6.99 × 10^{-5}	−7.47

The system III $\rightleftarrows$ I may be profitably compared with the system α-methylstyrene $\rightleftarrows$ α,α-dimethylbenzyl alcohol which has been studied by Peterson.[21] Peterson finds that the α-methylstyrene–dimethylbenzyl alcohol equilibrium favors the alcohol by nearly 10 to 1. He also reports that substituents in the ring have little influence upon the position of equilibrium. The rates of hydration and dehydration are very sensitive to the electronic character of the substituent. Related also is the recently reported rate of hydration of 2-anisylpropene by Schubert, Lamm, and Keeffe.[22]

The average equilibrium constant for the interconversion of III and I, obtained from data in 40–50% sulfuric acid, I/III = 18 (extrapolated to unit water activity), is very similar to the values observed by Peterson.[21] It is similar also to the values of the styrene–α-phenylethanol system studied by Schubert, Lamm, and Keeffe.[22] They find values near 40 for the alcohol to olefin ratio at equilibrium. Thus in all of these systems the conjugation of the double bond with the aromatic ring is an important factor,[23] but

(23) For isobutene–t-butyl alcohol, Lucas and Eberz, *J. Am. Chem. Soc.*, **56**, 1230 (1934), report that only 0.01% isobutene remains at equilibrium.

additional substituents and alkyl groups are of only secondary importance.

The rate of hydration of III and the rate of dehydration of I are markedly less than the rates[24] for the 2-phenylpropene–dimethylbenzyl alcohol system. The difference is clearly due to the inductive influence of the carboxyl group.

The Interconversion of I and II. Concurrently with the dehydration of I to form III, 3-phenyl-3-butenoic acid, there is dehydration to form II, *trans*-β-methylcinnamic acid. By making measurements, using initial rate techniques, of the initial increase in absorbance at 273 mμ, the rate of formation of II may be calculated. Data are summarized in Table IV.

Table IV. Rate of Formation of *trans*-β-Methylcinnamic Acid at 25.00°

H$_2$SO$_4$, %	$-H_0$	k_T, sec.$^{-1}$	log $k + H_0$
38.90	−2.33	0.56 × 10^{-5}	−7.58
45.13	−2.86	3.00 × 10^{-5}	−7.38
49.28	−3.31	9.47 × 10^{-5}	−7.33

The rate of formation of II from I is a strongly acid-catalyzed reaction, with a slope of log k *vs.* H_0 somewhat greater than unity, as has frequently been observed for other alcohol dehydrations proceeding by way of carbonium ion intermediates.[5,6,21,22]

It is also possible to start with II, and measure the initial rate of decrease in absorbance at 273 mμ in order to determine the rate of hydration of II. Data relating to this reaction are summarized in Table V.

Table V. Hydration of *trans*-β-Methylcinnamic Acid at 25.00°

H$_2$SO$_4$, %	$-H_0$	$10^5 k_{-T}$, sec.$^{-1a}$	log $k + H_0$
46.97	3.06	2.58	−7.65
49.30	3.31	4.60	−7.65
51.83	3.58	8.72	−7.64
54.20	3.83	18.0	−7.57
59.86	4.44	47.0	−7.77

^{a} All runs in duplicate.

The hydration reaction is acid catalyzed and shows very nearly unit slope *vs.* H_0. Such a correlation with the acidity function is similar to that observed in the proton attack on *cis*-cinnamic acid.[25] The interconversion of I and II shows that the dehydration rate of II and the dehydration of I to give the conjugated isomer II are very similar. The apparent equilibrium constant for this reaction, isolated from the other concomitant reactions of I, is very nearly unity.

This stands in substantial contrast to the equilibrium constant for the dehydration of β-hydroxy-β-phenylpropionic acid which was reported earlier from these laboratories.[26] Clearly the interference to coplanarity caused by the *cis* interaction of the methyl and carboxyl groups in II has resulted in a small quantitative

(24) These rates may be estimated from the ρ values reported by Peterson[21] and the rate given by Schubert, Lamm, and Keeffe[22] for 2-p-anisylpropene.
(25) D. S. Noyce, P. A. King, F. B. Kirby, and W. L. Reed, *J. Am. Chem. Soc.*, **84**, 1632 (1962).
(26) D. S. Noyce and C. A. Lane, *ibid.*, **84**, 1637 (1962).

shift in the energy balance between the alcohol and the related cinnamic acid.

A similar shift in the equilibrium balance between β-hydroxy acid and α,β-unsaturated acid upon introduction of an additional branching methyl group is reported by Pressman and Lucas.[27] Changing from the β-hydroxybutyric acid–crotonic acid system to the β-hydroxyisovaleric acid–dimethylacrylic acid system results in a substantial decrease in the relative stability of the unsaturated acid.

Comparison of Equilibrium Values [II]/[I] and [III]/[I]. When the optical density of a sulfuric acid solution of β-hydroxy-β-phenylbutyric acid reaches a maximum, the concentrations of the two unsaturated acids II and III may be calculated from the optical density values. The measured amount of CO_2 then allows the calculation of the concentration of the remaining hydroxy acid concentration, and consequently equilibrium constants $K_T = [II]/[I]$ and $K_\beta = [III]/[I]$ may be evaluated.

In 49.3% sulfuric acid at 25.00° 30% of the original hydroxy acid has decarboxylated by the time the pseudo-equilibrium is reached. Starting with a solution initially 3.14×10^{-5} M in I, the average values for II, 1.39×10^{-5} M, and for III, 0.10×10^{-5} M, are calculated from the observed absorbances at 243, 260, and 273 mμ. This leaves (I) 0.71×10^{-5} M. Thus, in 49.3% sulfuric acid the equilibrium values are $K_T = 1.96$ and $K_\beta = 0.141$.

These equilibrium constants may be compared with the values obtained from the initial rates of reaction of I, II, and III. The measured rate constants yield $K_T = k_T/k_{-T} = 2.06$ and $K_\beta = k_\beta/k_{-\beta} = 0.144$. It can be seen that the agreement is excellent.

Calculations in 46% sulfuric acid solution and in 40% sulfuric acid solution show similar agreement.

The Rate of Decarboxylation of I. With the simple hydration and dehydration reactions of I in hand, it is finally feasible to examine the rates of decarboxylation of I under a variety of conditions.

Measurements of the rate of decarboxylation have been made by a combination of methods and techniques. Volumetric determination of CO_2 evolution is severely limited in precision due to the very low solubility of I in the aqueous sulfuric acid media. Some measurements were made by this method. In other instances the amount of CO_2 evolved was determined gravimetrically (as $BaCO_3$).

As described above, the evolution of CO_2 from I in 50% sulfuric acid amounts to 30% of the theoretical amount after 300 min. More slowly thereafter the remaining CO_2 is evolved from the "pseudo-equilibrium mixture" of I, II, and III. In less concentrated sulfuric acid the pseudo-equilibrium point is reached more slowly; a larger fraction of I undergoes decarboxylation rather than dehydration. The best values for the rate of decarboxylation of I in sulfuric acid are given in Table VI. The precision of these results is not high;

(27) D. Pressman and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 2271 (1939); **62**, 2069 (1940).

perhaps the uncertainty is as large as 25%. Column four of Table VI lists the percentage of the theoretical amount of CO_2 evolved in the initial portion of the total course of the reaction.

Table VI. Rate of Decarboxylation of I at 25.00°

H_2SO_4, %	H_0	k_{CO_2}	CO_2, %
40.3	−2.44	1.1×10^{-5}	52
46.1	−2.96	2.5×10^{-5}	42
49.3	−3.31	3.5×10^{-5}	30

Using the separately determined rate constants k_β, $k_{-\beta}$, k_T, k_{-T}, and k_{CO_2} it is possible to compute the observed concentration of II as a function of time using either analog computer techniques or digital computer techniques.[28] Very satisfactory correspondence is obtained, both for the total concentration of II and for the total evolution of CO_2.

Thus the rate measurements described here adequately describe the behavior of this system. A few experiments served to show that cis-β-methylcinnamic acid is not a dynamic part of this chemical system. Introduction of cis-β-methylcinnamic acid into 50% sulfuric acid resulted in the observation that this compound reacts nearly ten times more slowly than II. This is apparently the result of the steric interference of the phenyl and carboxyl groups, resulting in a non-ideal geometry for the original proton attack to initiate hydration, resulting in a substantially lowered reactivity for cis-β-methylcinnamic acid.

Conclusions. Though the precision of these results is not as refined as might be desirable, nevertheless three conclusions are abundantly clear: (1) the decarboxylation is a reaction characteristic of the hydroxy acid; (2) the sensitivity of the rate of decarboxylation to sulfuric acid concentration is very low; and (3) decarboxylation will be the predominant reaction in dilute mineral acid solutions, while dehydration will be the predominant reaction in concentrated mineral acid solutions.

Further, though the rate of dehydration to form the nonconjugated isomer is similar to the rate of dehydration to form the conjugated isomer, very little β,γ isomer accumulates as it is very rapidly rehydrated. Thus it is permissible to largely ignore the β,γ isomer under all conditions except the very early portion of kinetic runs.