between pH 5.5 and 6.5. Above this value the pH dependency becomes smaller since the sulfite form becomes a sizable proportion of the total sulfite plus bisulfite in solution. Apparently rapid racemization subsequent to the rate-determining S$_N$2 step leads to the racemic product since characteristic inversion of configuration at the asymmetric center is not observed.

The observed pH dependency between 5.5 and 6.5 can be equivalently explained on the basis that the catecholate form of the drug reacts with bisulfite ion. This possibility certainly cannot be ruled out on the basis of the present study.

The second route is thought to be mediated through formation of a carbonium ion which is normally responsible for racemization of the drug in absence of bisulfite. This reaction, governed by rate constant k_1, does not appear to be hydrogen ion dependent, at least in the pH range employed, since the racemization rate studied in absence of bisulfite indicated a half-life of 118 hours at pH 4.0 and 130 hours at pH 4.9 and 84.5°. The carbonium ion formed can react with water to form the racemic compound or in presence of bisulfite or sulfite react to form the sulfonate.

The suggested nucleophilic attack by sulfite (or bisulfite) ion on the carbonium ion (k_3) must be very fast compared to the rate of reformation of epinephrine. This assumption seems entirely logical in view of the species involved and explains the observed zero-order dependency on bisulfite provided k_1 governs the rate-determining step.

Below pH 6, and in the presence of bisulfite, the derived rate equation IV may be simplified to

$$-d(Ep)/dt = k_4(Ep)(SO_3^{=}) + k_1(Ep) \qquad (V)$$

Epinephrine, pK_a 8.55,[4] exists predominantly as positively charged species over the pH range studied and the second ionization constant of sulfurous acid, $K_{a_2} = 6.24 \times 10^{-8}$ at 25° in dilute solution, fixes the concentration of sulfite for any added stoichiometric quantity of sulfur compound: $(SO_3^{=}) = S_{total}\,K_a/(H^+)$ where $(H^+) > K_a$.

In Fig. 6 theoretical points based on equation V and a K_a value of 1×10^{-7} are shown at widely spaced pH values. It is evident that the form of the equation is in good agreement with the observed experimental facts.[4]

Acknowledgment.—This study was supported in part by a grant from Parke, Davis and Co. of Detroit, Mich., and a grant from the Research Committee of the Graduate School from funds supplied by Wisconsin Alumni Research Foundation.

[4] M. M. Tuckerman, J. R. Mayer and F. C. Nachod, THIS JOURNAL, **81**, 92 (1959).

MADISON 6, WIS.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

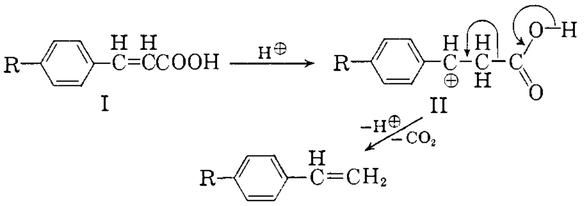
A Study of pH Dependence in the Decarboxylation of p-Hydroxycinnamic Acid[1]

BY LOUIS A. COHEN AND WILLIAM M. JONES

RECEIVED JULY 24, 1959

The rate of decarboxylation of p-hydroxycinnamic acid has been studied in aqueous media in the pH range 1–12. Of the several p-substituted cinnamic acids examined, the p-hydroxy compound is unusual in its ability to decarboxylate beyond pH 3. The rate of decarboxylation has been correlated with hydrogen ion concentration and with the concentrations of the various pH-dependent forms present in solution. Some evidence is presented to show that the principal decarboxylating species is the vinylog of the β-keto acid resulting from dienone–phenol tautomerism.

Although the thermal decarboxylation of substituted cinnamic acids is a common synthetic procedure,[2] decarboxylation in aqueous media has received only scant attention. The breakdown of o- and p-hydroxycinnamic acids by hot mineral acid was reported in 1889.[3] However, it was not until 1949 that a kinetic study of the influence of substituents on the rate of acid-catalyzed decarboxylation of cinnamic acids appeared.[4] Evidence then was presented that decarboxylation in strong mineral acid proceeds *via* an S$_E$2 mechanism[5] since the rate increases continuously with increasing acid strength. A β-carbonium ion II was considered a likely intermediate, the decarboxylation being facilitated by β-substituents which tend either to increase the electron density at Cα or to stabilize the β-carbonium ion by resonance.



From a consideration of σ-constants, it might be expected that hydroxy- or methoxycinnamic acids would decarboxylate with particular ease and, indeed, the relatively rapid breakdown of a p-methoxycinnamic acid in hot mineral acid has been reported.[6] In the course of another investigation in this Laboratory, p-hydroxycinnamic acid was found to be unstable, decarboxylation being observed over a wide pH range.

Buffered solutions of p-hydroxycinnamic acid (0.02 M) were decarboxylated at 100° at various

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[1] Second paper of a series on phenol–dienone tautomerism; for paper I, *cf.* L. A. Cohen, *J. Org. Chem.*, **22**, 1333 (1957).

[2] (a) T. W. Abbott and J. R. Johnson, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 440; (b) C. Walling and K. B. Wolfstirn, THIS JOURNAL, **69**, 852 (1947).

[3] W. v. Miller and F. Kinkelin, *Ber.*, **22**, 1715 (1889).

[4] W. S. Johnson and W. E. Heinz, THIS JOURNAL, **71**, 2913 (1949).

[5] H. Schenkel and M. Schenkel-Rudin, *Helv. Chim. Acta*, **31**, 514 (1948).

[6] W. S. Johnson and M. W. Miller, THIS JOURNAL, **72**, 511 (1950).

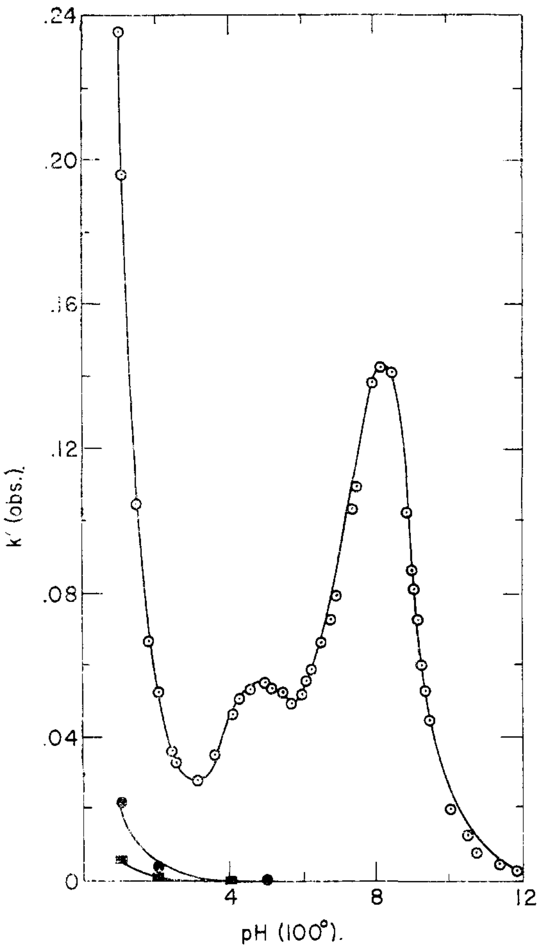
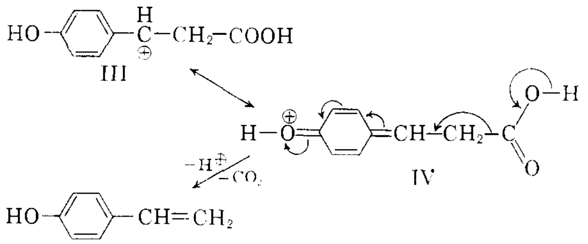
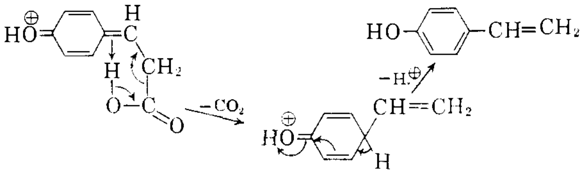


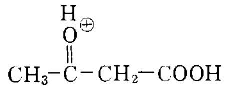
Fig. 1.—Variation in rate of decarboxylation with *p*H at 100° in water: ⊙, *p*-hydroxycinnamic acid; ●, *p*-methoxycinnamic acid; ■, cinnamic acid (in 50% 1-propanol).

*p*H values. The rate of the reaction was followed by the decrease in ultraviolet absorption at 310 mμ. Good agreement with (pseudo) first-order kinetics was observed for a large range of *p*H values. The variation of rate with *p*H is summarized in Fig. 1 together with the observed rates of decarboxylation for cinnamic and *p*-methoxycinnamic acids. *p*-Nitrocinnamic acid gave no indication of instability when heated at 100° at *p*H 1 for 16 hours. Obviously, *p*-hydroxycinnamic acid must be considered an unusual member of the series.

Although the σ-constant for *p*-hydroxy is only 33% more negative than for *p*-methoxy,[7] the magnitude of the decarboxylation rate for the phenolic acid suggests either a greatly increased resonance stabilization for the β-carbonium ion III or that IV, acting as the vinylog of a β-keto acid, makes a significant contribution to the structure of the decarboxylating species. The decarboxylation of acetoacetic acid below *p*H 2 has been found to be very nearly independent of *p*H,[8] probably because the H-bonded species VI decarboxylates more readily than the protonated form V.[9] The decarboxylation of IV may represent a mechanism which is not observed with simple β-keto acids.[10]

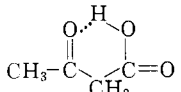






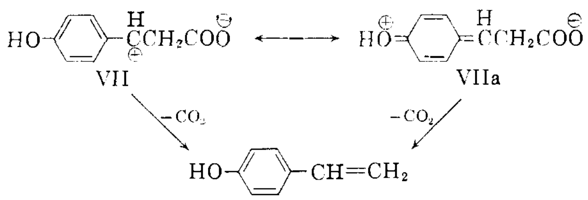
$$CH_3-\overset{\overset{H}{O^{\oplus}}}{\overset{\|}{C}}-CH_2-COOH$$

V

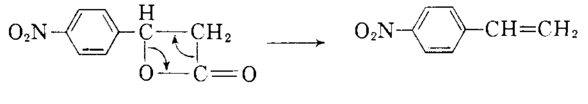


VI

Decarboxylation in the *p*H range 4–6 may be formulated as proceeding *via* the zwitterion VII, although the failure of *p*-methoxycinnamic acid to give any evidence for decarboxylation in this *p*H range directs attention to the canonical structure VIIa as the favored form for the reactive species.



In weak alkali, *p*-hydroxycinnamic acid decarboxylates fairly rapidly with the reaction rate dropping quite sharply beyond *p*H 9. Although there appears to be some evidence for the direct decarboxylation of the β-lactone derived from *p*-nitrocinnamic acid,[11] a mechanism involving β-addition of the carboxylate anion to the double bond and subsequent decarboxylation was rejected. The influence of *p*-substituents in such a mechanism should be the converse of that actually observed, *i.e.*, *p*-nitrocinnamic acid should decarboxylate most readily.[12] No decrease in ultraviolet intensity was observed when alkaline solutions of *p*-hydroxycinnamic acid were heated to 70°, implying the absence of a facile β-addition. In a decarboxylation experiment at *p*H 8.5 in the presence of benzylamine, no material containing an amide



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(7) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 72.

(8) E. M. P. Widmark, *Acta Med. Scand.*, **53**, 393 (1920).

(9) F. H. Westheimer and W. A. Jones, THIS JOURNAL, **63**, 3283 (1941).

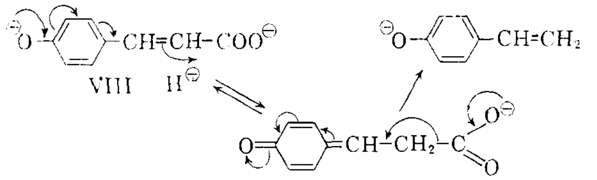
(10) A cyclic mechanism, kinetically indistinguishable from that proposed above, may be formulated (*cf.* R. T. Arnold, O. C. Elmer and R. M. Dodson, *ibid.*, **72**, 4359 (1950))

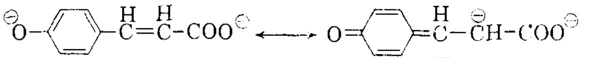
(11) A. Basler, *Ber.*, **16**, 3005 (1883).

(12) E. J. Corey and G. Fraenkel, THIS JOURNAL, **75**, 1171 (1953).

function could be detected, as might be expected to arise from aminolysis of a β-lactone.

It is proposed that protonation of the dianion VIII leads to the quinonemethine IX which undergoes rapid decarboxylation. The ultraviolet spectrum of *p*-hydroxycinnamic acid shows an alkaline shift of 35 mμ (310 → 345 mμ), which may be taken to indicate a partial contribution of X to the resonance hybrid of the phenolate anion. In the case of 3,5-di-*t*-butyl-4-hydroxycinnamic acid, addition of alkali produces a yellow solution and an alkaline shift of 70 mμ (310 → 380 mμ), suggesting an even greater contribution of the quinonemethine form XII. It might be expected that the introduction of *o*-*t*-butyl groups would favor the formation of XII, which offers the least steric hindrance to ionic solvation.[1] At *p*H 8.5, XI was found to decarboxylate 2.5 times as fast as *p*-hydroxycinnamic acid, providing additional support for the quinonemethine pathway. Although the decarboxylation of acetoacetic acid has been shown to be catalyzed specifically by primary amines,[13] no such special effect was observed in the present case. Decarboxylation in aqueous benzylamine or pyridine corresponded approximately in rate to that observed in a buffer solution of the same *p*H.


VIII IX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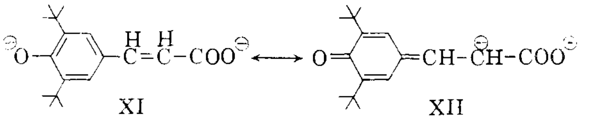
XI XII

In attempting to correlate the observed reaction rates with hydrogen ion concentration, the graphic methods employed by Brown, Elliott and Hammick for trihydroxybenzoic acid[14] failed to give straight line plots in any *p*H range. Assuming the absence of any unimolecular decomposition or of a bimolecular reaction involving water, the over-all rate may be expressed as the sum of three contributing reactions, each involving a separate species

$$k_{obs} = k_1[H_3O^+]^{n_1}[\alpha_1] + k_2[H_3O^+]^{n_2}[\alpha_2] + k_3[H_3O^+]^{n_3}[\alpha_3] \quad (1)$$

where

α_1 = fraction of undissociated acid
α_2 = fraction of monoanion
α_3 = fraction of dianion
n = order of hydronium ion in each participating reaction

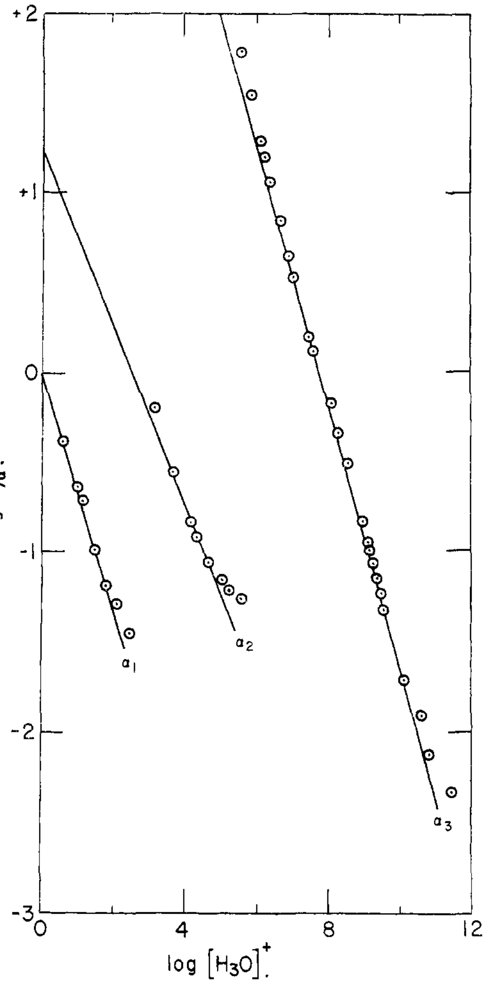

Fig. 2.—Graphical determination of *n* and *k* for each ionic species of *p*-hydroxycinnamic acid.

Assuming, further, that each species contributes principally to the rate in the region of the corresponding maximal rate, the expression may be simplified into

$$k_{obs} = k_i[H_3O^+]^{n_i}[\alpha_i] \text{ and} \quad (2)$$

$$\log\left[\frac{k_{obs}}{\alpha_i}\right] = \log k_i + n_i \log [H_3O^+] \quad (3)$$

By plotting log $[k_{obs}/\alpha_i]$ against log $[H_3O^+]$, n_i is obtained as the slope and log k_i as the intercept. The resulting straight-line plots are shown in Fig. 2 and the derived values in Table I.

TABLE I

GRAPHICAL DETERMINATION OF n_i AND k_i

α_i	n_i	k_i
α_1	2/3	1.05
α_2	1/2	16.5
α_3	2/3	1.4×10^{5}[a]

[a] This value was obtained by solution of equation 3 using the value for n_3 obtained graphically and averaging the resulting *k*-values for a number of points in the region of *p*H 8-9.

By substitution of these values into equation 1, the variation in total rate of decarboxylation with *p*H may be calculated, the results providing a good agreement with the curve of Fig. 1. A reasonable fit to the experimental curve was achieved only with fractional values for the order of hydronium ion.

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(13) K. J. Pedersen, THIS JOURNAL, **60**, 595 (1938).

(14) B. R. Brown, W. W. Elliott and D. L. Hammick, *J. Chem. Soc.*, 1384 (1951).

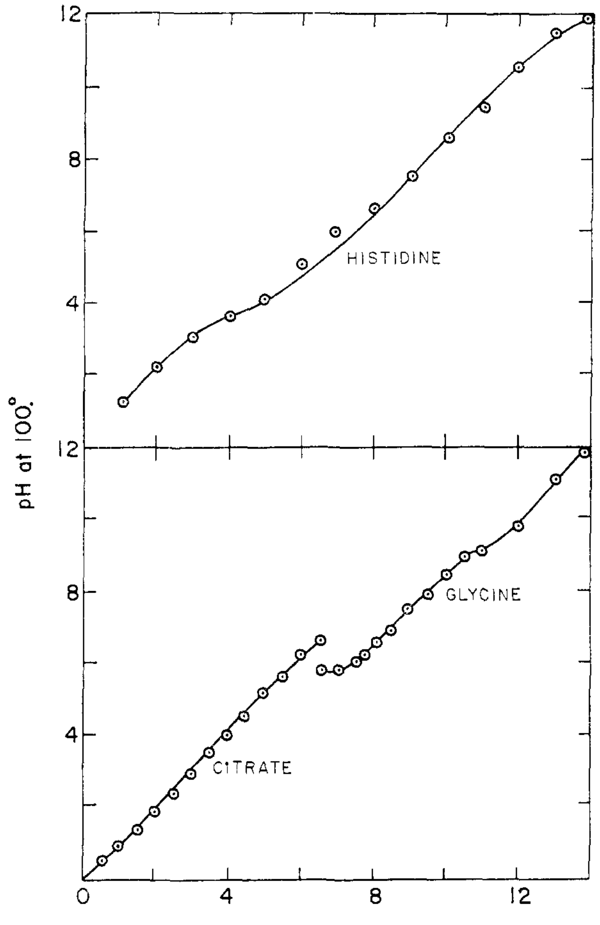

Fig. 3.—Influence of temperature on the *p*H values of buffer solutions (0.25 *M* buffer–0.75 *M* KCl).

The significance of the fractional exponents obtained by calculation is not apparent and suggests a greater complexity to the reaction than is here assumed. The use of unit exponents for hydrogen ion concentration in the calculations failed to give maxima and minima in the rate/*p*H curve.

Preliminary experiments show that *p*-dimethylaminocinnamic acid also decarboxylates with a complex *p*H dependence. In view of its tautomeric possibilities, such behavior is not unexpected. Unfortunately, the low solubility of the amino acid in the region of its isoelectric point complicates the measurement of decarboxylation rates.

Experimental

Materials.—Commercial cinnamic and *p*-nitrocinnamic acids were recrystallized from alcohol-water. Commercial *p*-hydroxycinnamic acid was recrystallized from hot water after decolorization with charcoal, m.p. 214–215°. *p*-Methoxycinnamic acid was prepared by the Knoevenagel condensation[15] and crystallized from hot water, m.p. 171–172°. *p*-Dimethylaminocinnamic acid, prepared according to Walling and Wolfstirn,[2b] was crystallized from ethanol, m.p. 218–219°. 3,5-Di-*t*-butyl-4-hydroxycinnamic acid[16] was freed of colored impurities by chromatographing a benzene solution on acidic alumina and recrystallizing the product from benzene–ligroin, m.p. 219–220°.

Buffers.—These various mixtures were used for the indicated *p*H ranges: *p*H 1.0–6.5, citric acid (0.25 *M*) + potassium chloride (0.75*M*); *p*H 6.5–13.0, glycine (0.25 *M*) + potassium chloride (0.75 *M*); *p*H 1.0–13.0, histidine (0.25 *M*) + potassium chloride (0.75 *M*).

Rate Measurements.—Solutions (0.02 *M*) were prepared by adding 2 ml. of 0.5 *M* *p*-hydroxycinnamic acid in dioxane to 48 ml. of the appropriate buffer.[17] Solutions then were adjusted to the desired *p*H by the addition of either concentrated hydrochloric acid or solid potassium hydroxide.[18] The solutions were immersed in an oil-bath at 120° and 1-ml. samples withdrawn at various time intervals. A zero time sample was taken as soon as refluxing began. No measurable decrease in ultraviolet intensity was observed in the time necessary to heat the solutions to reflux. The samples were diluted to 50 ml. with a mixture of ethanol–0.1 *N* hydrochloric acid (1:1) and the ultraviolet intensity at 310 mμ measured after appropriate dilution with ethanol. The reaction mixtures were cooled after 50–80% decarboxylation and the *p*H's measured. For purposes of calculation, the *p*H was taken as the average of the initial and final readings. Several runs, in which the change in *p*H was greater than 0.1 unit, were rejected. None of the buffer mixtures contributed significantly to ultraviolet absorption in the region of interest. By permitting decarboxylation to proceed to completion at various *p*H's, it was demonstrated that the contribution of products to 310 mμ absorption was negligible. Several runs between *p*H 7 and 13 were repeated using phosphate and borate buffers. Kinetic results were essentially in agreement with those in glycine or histidine buffers, rendering unlikely an amine catalysis of decarboxylation.

The decarboxylation of *p*-methoxycinnamic acid, as well as of 3,5-di-*t*-butyl-4-hydroxycinnamic acid, was followed in the same way. In the latter case, the rate of decarboxylation was measured only at *p*H 8.5, the reaction being conducted under nitrogen. The decarboxylation of cinnamic and of *p*-nitrocinnamic acids was followed at 275 and at 300 mμ, respectively. For solubility reasons, these acids were studied in 50% aqueous 1-propanol at *p*H's below 6.0.[19] Since the ultraviolet maximum of *p*-dimethylaminocinnamic acid occurs at 265 mμ in acidic ethanol, reaction samples were diluted with ethanol–0.1 *N* sodium hydroxide (1:1) and changes in the alkaline maximum at 335 mμ were followed.

Isolation of Products.—*p*-Hydroxystyrene could be isolated only as a polymer[20] from acidic or alkaline media after adjustment of the *p*H to 7.0 and extraction with methylene chloride. The material was identified by its infrared spectrum, which showed the appropriate phenolic absorption but was devoid of carbonyl bands. In several runs the extent of decarboxylation based on decrease in ultraviolet intensity was compared with the weight of isolated material, the maximum discrepancy in yield being about 10%. The decarboxylation of *p*-methoxy- and of *p*-dimethylaminocinnamic acids led to oily materials which were free of carbonyl absorption in the infrared but were not investigated further.

Results and Calculations.—In order to correlate rates of decarboxylation at 100° with hydrogen ion concentration, all *p*H values were corrected to 100°. Buffer solutions containing the various cinnamic acids were adjusted to a series of *p*H values, heated to 100° and the *p*H measured again. The observed changes in *p*H for the systems containing *p*-hydroxycinnamic acid are recorded in Fig. 3 (the same changes were observed in the absence of the cinnamic acid).

By plotting log I_0/I against time (hr.), slopes were determined graphically for each *p*H value. First-order rate constants (hr.$^{-1}$) were calculated as 2.3 × slope and are plotted in Fig. 1 against *p*H (at 100°).

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(15) E. Knoevenagel, *Ber.*, **31**, 2606 (1898).

(16) T. H. Coffield, A. H. Filbey, G. C. Ecke and A. J. Kolka, This Journal, **79**, 5023 (1957).

(17) Histidine buffer was used interchangeably with glycine or citric acid with comparable results.

(18) All *p*H measurements were performed on a Beckman Zeromatic *p*H meter, using electrodes serviceable at 100°.

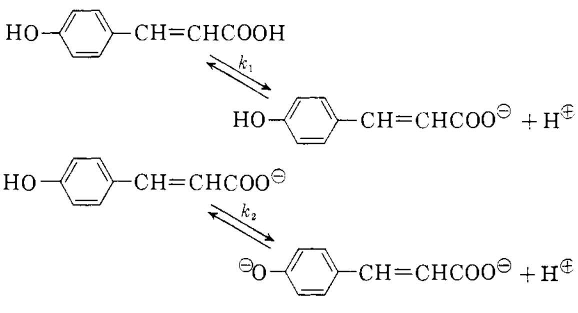
(19) Although the solvent system has been modified in these two cases, thereby affecting the dielectric constant of the medium, the changes in rate probably would be very small in comparison with those of *p*-hydroxycinnamic acid in water.

(20) *Cf.* H. Schmid and P. Karrer, *Helv. Chim. Acta*, **28**, 722 (1945).

Concentration of the three species at each hydrogen ion concentration was calculated by use of the relationships

$$\alpha_1 = H^2/M;\ \alpha_2 = K_1H/M;\ \alpha_3 = K_1K_2/M$$

where $M = H^2 + K_1H + K_1K_2$ and α_1 = concentration of undissociated acid, α_2 = concentration of monoanion, α_3 = concentration of dianion, H = hydrogen ion concentration and K_1 and K_2 are constants based on the consecutive equilibria



Dissociation constants at 100° were determined experimentally. The first dissociation of *p*-hydroxycinnamic acid at 25° has been measured as 2.34×10^{-5}.[21] A solution of the acid (0.02 *M*) was adjusted to *p*H 4.80 and heated to 100°, whereupon the *p*H decreased to 4.63. From the apparent ionization at 25°, K_1 at 100° was calculated to be 3.41×10^{-5} and $\Delta H_{\text{ion}} = 1390$ cal./mole. From titration data at 25°,[22] the second dissociation constant (apparent) for *p*-hydroxycinnamic acid was found to be 3.1×10^{-10}. A solution, adjusted to *p*H 9.50 at 25°, was observed to drop to *p*H 8.57 at 100°. By calculation, K_2 at 100° was found to be 2.70×10^{-9} and $\Delta H_{\text{ion}} = 6530$ cal./mole. Calculated rate constants then were obtained as described by equations 1 and 3 (see Discussion).

[21] W. A. Roth and R. Stoermer, *Ber.*, **46**, 260 (1913).

[22] The procedure described by T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1954), for apparent *pK* values was used.

BETHESDA, MD.

[CONTRIBUTION FROM CALIFORNIA RESEARCH CORPORATION]

Oxidation of Organic Compounds with Aqueous Sulfate

BY WILLIAM G. TOLAND

RECEIVED AUGUST 14, 1959

A new oxidizing agent, inorganic sulfate, has been found to have wide utility in organic chemistry. It is most useful for the conversion of methyl groups to carboxylates. Somewhat related to the use of sulfur and a base and the Willgerodt reaction, it is superior in terms of oxidizing capacity per unit weight, simplicity of handling, economy and ease of product isolation. A singular requirement in its application is the presence of a lower valence state of sulfur to initiate the reaction.

Introduction

Previously it was shown that by the use of sulfur and an aqueous base many organic compounds can be oxidized to carboxylic acids.[1] One of the simplest systems for study is the oxidation of toluic acid with sodium polysulfide, ammonium polysulfide or sodium hydroxide plus sulfur.[2] There are several drawbacks to such systems. Either polysulfide must be specially prepared, or a heterogeneous system must be used involving a separate sulfur phase. The quantities of sulfur required may outweigh the compound to be oxidized; for instance, to oxidize one mole of xylene (106 g.) requires 6 moles of sulfur (192 g.). In turn, 6 moles of H_2S are generated which, if not neutralized, limit the capacity of any reaction vessel owing to the large gas volume or the high pressure generated.

A solution is suggested by the behavior of the sodium hydroxide–sulfur mixtures on heating. Disproportionation occurs to dissolve the sulfur completely. Yields of oxidation products indicate that all of this sulfur can be consumed to give H_2S. Thus, whatever disproportionation occurs must be reversible under certain conditions, or the disproportionated products must be equally effective oxidants. The literature gives many examples of such disproportionations of sulfur in basic solutions.[3] Products contain not only sulfide and polysulfide but sulfite and thiosulfate in varying proportion as a function of the ratio of reactants and temperature. It would thus appear reasonable to utilize sulfite or thiosulfate as homogeneous oxidant with greater oxidizing capacity than free sulfur and possibly with greater reactivity. This is in contrast to the use of thiosulfate as a catalyst, described by Pattison and Carmack[4]

$$\mathrm{ArCH_3 + 3S + NH_4OH + H_2O \longrightarrow ArCO_2NH_4 + 3H_2S} \quad (1)$$

$$\mathrm{ArCH_3 + (NH_4)_2SO_3 \longrightarrow ArCO_2NH_4 + H_2O + NH_4SH} \quad (2)$$

$$\mathrm{ArCH_3 + {}^3/_4(NH_4)_2S_2O_3 \longrightarrow ArCO_2NH_4 + {}^1/_4H_2O + H_2S + {}^1/_2NH_4SH} \quad (3)$$

Results

Experimental results with the various valence states of sulfur as oxidants are shown in Table I. One of the puzzling features of the oxidations with sulfur is the variation of conversions. In the study of variables, a correlation was found between conversions and the ratio of base to oxidant. The fate of the sulfur finally was established as its disproportionation to sulfate, a reaction not heretofore recognized, although Priestley, in 1775, noted

[1] W. G. Toland, D. L. Hagmann, J. B. Wilkes and F. J. Brutschy, THIS JOURNAL, **80**, 5423 (1958).

[2] W. A. Pryor, *ibid.*, **80**, 6481 (1958).

[3] (a) H. V. Tartar and C. Z. Graves, *ibid.*, **46**, 574 (1924); (b) E. R. Bertozzi, U. S. Patent 2,796,325, June 18, 1957; (c) E. Schulek and E. Koros, *Acta Chim. Acad. Sci. Hung.*, **3**, 125 (1953).

[4] D. B. Pattison and M. Carmack, THIS JOURNAL, **68**, 2033 (1946).