Preparation of dl-endo-Fenchyl Alcohol. The reduction of fenchone was carried out on a preparative scale to test the utility of the procedure for such preparations. In a 1-l. flask was placed 750 ml. of distilled tetrahydrofuran, and 0.4 mole of lithium aluminum hydride was added. The mixture was stirred overnight with a magnetic stirrer. The solids were allowed to settle and an aliquot of the clear solution was analyzed for dissolved hydride by the usual procedure. A sufficient quantity of the clear solution was placed in a 1-l., three-neck flask, fitted with condenser, stirrer, and addition funnel, to provide 0.3 mole of the reagent. The solution was cooled to 0° and 0.9 mole of methanol was slowly added (exothermic reaction) as the hydrogen evolved was vented. Then 35 g. (0.25 mole) of *dl*-fenchone was added from the dropping funnel at such a rate that the temperature could be maintained at approximately 0°. After addition was complete, the solution was stirred at 0° for 1 hr. Residual hydride was then destroyed by the slow addition of water. The reaction mixture was then transferred to a separatory funnel, ether was added, and then the mixture was treated with a saturated solution of sodium potassium tartrate. The organic phase was separated, the aqueous layer was extracted with ether, and the combined ether extract was dried over anhydrous magnesium sulfate. The solvents were removed on a rotary evaporator. Distillation provided 30.7 g., 80% yield, of *dl-endo*-fenchyl alcohol, b.p. 43–45° (1 mm.), 97% isomerically pure by gas chromatographic examination, m.p. *p*-nitrobenzoate 93–94.5° (lit.[26] m.p. 94–95°).

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Intramolecular Catalysis of Ketone Enolization in o-Acylbenzoic Acids[1]

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The kinetics of enolization of o-isobutyrylbenzoic acid has been measured in aqueous solution from pH 0 to 11 at 25°. Enolization rates were calculated from spectrophotometrically determined rates of iodination. Four kinetic terms contributed to the enolization: (1) the reaction of hydronium ion and the undissociated carboxylic acid; (2) the reaction of hydroxide ion and the carboxylate ion; (3) the reaction of the undissociated carboxylic acid; and (4) the reaction of the carboxylate anion. Of these four reactions, the last is the most important, being the predominant reaction from pH 2.5 to 10. In this region, the rate of the enolization reaction is dependent on the ionization of a group of $pK_a = 4.4$ and is unaffected by external buffers. The facile catalysis of enolization in the carboxylate anion can be mechanistically interpreted in terms of intramolecular general basic catalysis by the o-carboxylate ion, or alternatively in terms of intramolecular general acidic catalysis by the o-carboxylic acid group in a reaction with hydroxide ion. The former interpretation is preferred on kinetic and steric grounds. Intramolecular catalysis by o-carboxylate ion corresponds in efficiency to a concentration of the corresponding intermolecular catalyst of the order of 50 M. This intramolecular catalysis of enolization may serve as a model for the intracomplex catalysis of enolization of dihydroxyacetone phosphate by the enzyme aldolase.

Introduction

The initiating step of many organic reactions, synthetic and biochemical, is the transfer of a hydrogen atom from a carbonyl compound to a base, leading to the formation of an enolate ion or enol. Catalysis of enolization has been one of the most thoroughly studied of all organic catalytic processes.[3,4] Recent work has attempted to extend our understanding to enzyme-catalyzed reactions which depend on enolization.[5-7] If an enzymatic group of an enzyme–substrate complex catalyzes the enolization of the substrate, the process may be described as an intracomplex catalysis. A suitable model for the elucidation of possible mechanisms of intracomplex catalysis has been the use of intramolecular catalysis.[8] Therefore, it seemed desirable to examine the intramolecular catalysis of enolization.

In classic work on the mechanism of enolization, Ingold, Wilson, and Hsu[9] compared the rates of racemization and bromination of 2-(o-carboxybenzyl)-indanone, in which intramolecular catalysis of enolization by the carboxyl group could occur, but they did not discuss this possibility. The enolization of a number of aliphatic ketones containing potential intramolecular catalytic groups has been investigated. Both the bromination of levulinic acid[10] and the

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iodination of levulinic acid in the presence of glycine catalyst[11] have been reported, but insufficient data are available to be interpreted in terms of intramolecular catalysis. During the course of this work, a report by Bell and Fluendy[12] on intramolecular catalysis in the enolization of a series of aliphatic keto acids appeared. In all these flexible aliphatic systems it would be expected that intramolecular catalytic effects would be smaller than in the stereochemically fixed o-acylbenzoic acids, the subject of the present research.

This report presents data on the enolization of o-acylbenzoic acids, compounds in which a catalytic function is in forced proximity to an enolizable hydrogen atom. The efficacy of intramolecular catalysis was investigated from a comparison of the rates of enolization of the keto acids with those of suitable reference ketones which undergo intermolecular catalysis, and also from the pH dependence of enolization.

Experimental Section

Materials. o-Acetylbenzoic acid (Aldrich Chemical Co.) was purified by successive recrystallizations from benzene and water, m.p. 117.5–119.5° (lit. m.p. 114–115°[13] and 115–117°[14]). o-Isobutyrylbenzoic acid[15] was recrystallized from water, m.p. 121.8–122.5° or from benzene–hexane and from water, m.p. 122.8–124.2° (lit.[15] m.p. 121.5–122.5°). The two samples yielded concordant kinetic results.

For kinetic measurements, Eastman Spectro Grade acetone was used directly. Water was redistilled from alkaline potassium permanganate, or with a Corning still, Model AG-2. All other reagents were of analytical grade purity where available. Buffer solutions were prepared[16,17] by partial neutralization of acetic acid, sodium dihydrogen phosphate, sodium bicarbonate, or disodium phosphate solutions with 1.07 M sodium hydroxide solution, or by combining two appropriate buffer components.

Iodine–triiodide solutions were titrated against standard sodium thiosulfate,[18] stabilized by inclusion of 0.05–0.1% chloroform, using a 1% starch solution containing 20% sodium chloride.[19] Iodide solutions were analyzed by oxidation to iodine and titration against standard thiosulfate[20] after addition of *ca.* 0.4 g. of potassium iodide to secure a sharp end point.[21]

Kinetic Method. Rates of enolization were determined by following spectrophotometrically the rates of disappearance of iodine and/or triiodide ion from aqueous solutions of the ketones. Since both iodine and triiodide ion are capable of halogenating enols,[22]

the rate of disappearance of ketone from solutions containing both species must be equal to the combined rates of halogenation. This rate was determined as the rate of decrease of absorbance at the iodine-triiodide isosbestic point near 470 mμ (ϵ 675 ± 25) or more conviently as the rate of disappearance of only the triiodide ion at the wave length of its intense maximum, 351 mμ (ϵ 2.6 ± 0.1 × 10⁴).[23] Proportionality of the halogenation rate to triiodide ion concentration required the presence of sufficient iodide ion to make the ratio of triiodide ion to free iodine concentration constant; a 60-fold excess of iodide ion usually was employed.

The kinetic experiments were carried out in a Cary Model 14PM recording spectrophotometer equipped with a thermostated cell compartment. Zero-order kinetics was followed using a ketone concentration large enough to be invariant during the course of reaction. With acetone or acetophenone, this was accomplished using initial concentrations of triiodide ion equal to or less than 1% of the ketone concentration. With o-isobutyrylbenzoic acid, it was more convenient to use a ketone concentration only ten times larger than the stoichiometric iodine concentration, but to observe the disappearance of only the first 10% of the triiodide ion. The latter technique was used to minimize the effect of an initial curvature in the zero-order plots of this reaction.

The validity of the kinetic method was demonstrated in the iodination of acetone in acetate buffers, giving values of the catalytic constants of acetic acid and acetate ion within 10% of those reported in the literature.[24,25]

In base-catalyzed halogenation of methyl ketones, multiple halogenation is possible. The introduction of a halogen atom increases the rate of halogenation leading to successive halogenations of the same molecule. Therefore, in the experiments described above with acetone, initial rates were measured by observing halogenation of no more than 0.3% of the ketone.

In the determination of the rate of iodination of the keto acids 3.00 ml. of a solution containing the keto acid, a buffer, sodium iodide, and enough sodium perchlorate to adjust the ionic strength to 0.50 was placed in a 1-cm. cuvette, covered with a Teflon stopper, and thermostated for at least 15 min. in the cell compartment of the Cary spectrophotometer. The reaction was started by addition of 10 μl. of a solution 0.010 M in iodine and 0.050 M in potassium iodide, held on the tip of a stirring rod. The cuvette was covered with the Teflon stopper during the reaction.

Reactions at pH 0 were carried out using iodine prepared by addition of sodium iodide solution to one containing excess potassium iodate to prevent the rapid acid-catalyzed autoxidation of iodide ion.[26] The reactions were followed at 461.0 mμ, the absorption maximum of iodine measured under the reaction conditions (ϵ 740).

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The zero-order iodination of o-isobutyrylbenzoic acid was complicated by the incursion of an initial non-linear, decelerating reaction. A satisfactory explanation for this curvature appears to be provided by the incursion of a relatively fast bimolecular reaction of an impurity in the keto acid with iodine and/or triiodide ion. The difference in total iodine concentrations represented by the real intercept and the intercept extrapolated from the linear portion of the reaction gave the percentage of impurity as 0.1% of the keto acid concentration. The enol present in the reactant could not account for the impurity because its equilibrium concentration in the keto acid is probably less than $10^{-3}\%$[27] and the rate constant for the iodination of an enol is of the order of 10^5–10^6 M^{-1} sec.$^{-1}$,[22] while the rate constant calculated from the initial curvature was of the order of 5×10^3 M^{-1} sec.$^{-1}$.

Lactol–Keto Acid Equilibria. The ring–chain tautomerism exhibited by o-acylbenzoic acids may be investigated by measurement of infrared carbonyl stretching frequencies. The lactol carbonyl group behaves like that of similarly constituted lactones, while the free ketone and carboxyl (carboxylate) groups exhibit characteristically normal and distinct stretching frequencies.[28] In the solid state, in nonpolar solvents, and even in aqueous solution, o-acylbenzoic acids exist to a large extent in the cyclic lactol form.[29] On the other hand, o-acylbenzoate ions in aqueous solution exist predominantly, if not exclusively, in the noncyclic form.[29] Studies of the infrared absorption bands of o-acetylbenzoic acid and o-isobutyrylbenzoic acid in deuterium oxide solvent are consistent with these previous observations: o-acetylbenzoic acid, 1764 and 1748 cm.$^{-1}$; o-acetylbenzoate ion, 1675 and 1563 cm.$^{-1}$; o-isobutyrylbenzoic acid, 1748 cm.$^{-1}$; o-isobutyrylbenzoate ion, 1678 and 1563 cm.$^{-1}$.

An attempt was made to measure the rates of approach to lactol–keto acid equilibrium upon acidification of the o-acylbenzoate anions, using a stopped-flow spectrophotometer.[30] Equimolar solutions of salts of the keto acids and perchloric acid were mixed in the apparatus and observed at 250 and 280 mμ. In all cases, the changes were too fast to be measured, placing a lower limit of 100 sec.$^{-1}$ on the over-all rate constant for isomerization.

pK_a Measurements. The pK_a of o-isobutyrylbenzoic acid was determined in two ways: from the titration curve of the acid using a Radiometer Titrigraph, and from spectrophotometric measurement of the concentrations of neutral and anionic forms of the keto acid, using a Cary 14 spectrophotometer. The former method gave $pK_a = 4.55 \pm 0.06$ at essentially zero ionic strength; the latter method gave $pK_a = 4.61 \pm 0.16$ at essentially zero ionic strength and $pK_a = 4.23 \pm 0.22$ at $\mu = 0.5$.

The pK_a of o-acetylbenzoic acid was determined by automatic titration using the Titrigraph: $pK_a = 4.02 \pm 0.12$ at $\mu = 0$; and by half-ionization: $pK_a = 4.12 \pm 0.02$ ($\mu = 0.02$) (lit. $pK_a = 4.13, 4.14$[31,32]).

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Reaction Product. The initial product of the iodination of o-isobutyrylbenzoate ion would be expected to be the iodo ketone I, but it is apparent that this compound may react further to produce the lactone, II. In order to verify the step being measured in the kinetic
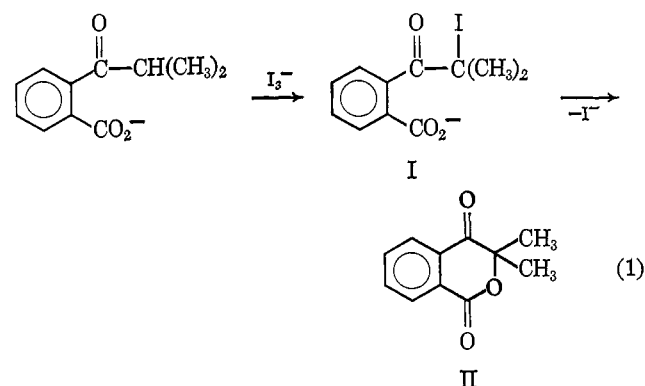
experiments, the preparations of I and II were attempted, the relative rates of formation of I and II were determined, and the identification of the product under conditions of the kinetic experiments was carried out.

In order to prepare the iodo ketone I, it is necessary to suppress the conversion of I to II, by protonation of the intramolecular nucleophile, carboxylate ion. However, when this is done by working in acidic solution, it is not possible to iodinate the ketone because of the unfavorable equilibrium. Therefore, the corresponding bromo ketone was prepared by bromination of o-isobutyrylbenzoic acid in ether solution containing trifluoroacetic acid as catalyst. The product was recrystallized from carbon tetrachloride and hexane, m.p. 92.5–94.0°.

Anal. Calcd. for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09; Br, 29.48. Found: C, 48.88; H, 4.08; Br, 29.56.

The anion of the bromo keto acid rapidly lost bromide ion to give a halogen-free product, 3,3-dimethyl-1,4-isochromanedione (II). The process could be conveniently followed on the Cary spectrophotometer at the absorption maximum of II, 302 mμ (ϵ 2130), giving a first-order rate constant for the intramolecular nucleophilic displacement of 0.2 sec.$^{-1}$. A crude comparison of this rate constant with that of α-bromoisobutyrophenone and external carboxylate ion under the same conditions indicates that 10^3 M carboxylate ion would be necessary for the rate of the intermolecular process to equal that of the intramolecular process measured here. In keeping with the characterization of the reaction as an intramolecular displacement by carboxylate ion, the rate was observed to decrease with pH, and a plot of the observed rate constant *vs.* pH was a sigmoid curve with an inflection point at pH 4.59, a reasonable value for the pK_a of the bromo keto acid. Furthermore, the conversion of the bromo keto acid to the lactone is at least 10^4 times faster than the intramolecular enolization measured here, over the entire pH range. The lactonization of the iodo keto acid would be expected to be even faster, and thus the slow step of eq. 1 would be the iodination proper, while the product of the reaction would be expected to be the lactone, II.

3,3-Dimethyl-1,4-isochromanedione (II) was synthesized most readily from o-isobutyrylbenzoic acid and

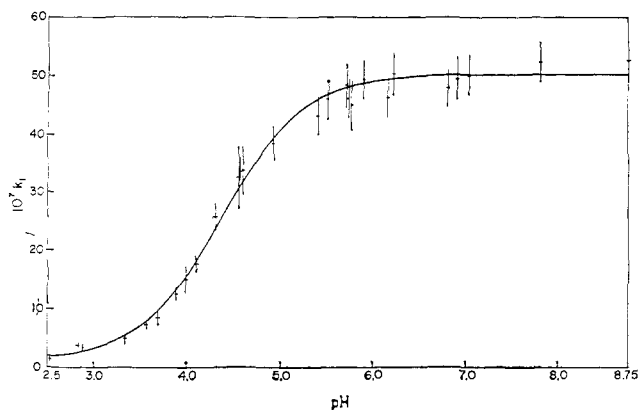(32) J. Tirouflet, *Compt. rend.*, 236, 1426 (1953).

Figure 1. The kinetics of iodination of o-isobutyrylbenzoic acid at 25.0° in aqueous solution, $\mu = 0.50$.

iodine (10% molar excess) in a mixture of pyridine and water. The solution was heated on the steam bath for 1 hr., becoming partly decolorized. Decolorization of the mixture was completed by addition of sodium bisulfite solution, and the solution was concentrated until an oily phase separated. Pyridine was removed by acid washing and the product (86% yield, m.p. 60–63°) was finally purified by recrystallization from hexane, m.p. 63.5–64.5°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.61; H, 5.30.

The lactone was spectrophotometrically shown to be the product of iodination of o-isobutyrylbenzoic acid under the conditions of the kinetic experiments. A reaction mixture containing the keto acid (3.20 × 10^{-4} M), iodide ion (0.050 M), sodium perchlorate (ionic strength 0.5), and 2.9 × 10^{-4} M in total iodine content in a phosphate buffer (0.20 M, pH 6.22) was stored in the dark for 10 days. The pH and reaction time were chosen to produce the maximum yield of lactone, treating it as an unstable intermediate between consecutive first-order reactions of enolization ($k = 5.0 × 10^{-6}$ sec.$^{-1}$) and hydroxide ion catalyzed hydrolysis of the lactone ($k = 4.5$ M^{-1} sec.$^{-1}$). The lactone product determined spectrophotometrically at 302 mμ was 2.9 × 10^{-4} M, corresponding to a quantitative yield. In one experiment the lactone product was isolated by extraction with ether, affording a crystalline product (55%), m.p. 62–64°, mixture melting point with authentic lactone 63–65°.

Results

The kinetics of the iodination of o-isobutyrylbenzoic acid was determined at a number of pH values using various concentrations of substrate and iodine and various buffer systems. Most of the kinetic data, recorded at 351.0 mμ, were treated in the following manner. The experimental zero-order decrease in triiodide ion absorbance was related to the first-order rate constants of the reaction (k_1) in the following manner. The rate of disappearance of iodine at this wave length is

$$-d[I_2]_T/dt = k_1[\text{ketone}] \qquad (2)$$

Since the rate-determining step of iodination is the formation of enol, the rate is independent of the iodine concentration.[4] Iodine is present both as free iodine and triiodide ion, in equilibrium with each other.

$$[I_2]_T = [I_2] + [I_3]^- \qquad (3)$$

$$K_{I_3^-} = ([I^-][I_2])/[I_3]^- \qquad (4)$$

The triiodide dissociation constant, $K_{I_3^-}$, was expected to be independent of the buffer medium employed. This hypothesis was tested by the determination of this equilibrium constant in water, sodium perchlorate, perchloric acid, as well as in five buffer systems, potassium acid phthalate (0.04 M), acetate (0.2 M, pH 4.7), phosphate buffer (0.2 M, pH 5.6), phosphate buffer (0.2 M, pH 6.8), and carbonate buffer (0.2 M, pH 9.69). In all solutions except the carbonate buffer, $K_{I_3^-} = 1.5 \pm 0.2 × 10^{-3}$ M. Analysis of the data from the carbonate buffer was complicated by the possible hydrolysis of iodine, and its deviant behavior was therefore ignored, especially since the rate constant of iodination, k_1, is not sensitive to the exact value of $K_{I_3^-}$.

If the iodide ion concentration is a constant (see the Experimental Section) then eq. 2 may be transformed to eq. 5, using eq. 3 and 4. Since the ketone concentration

$$k_1[\text{ketone}] = (1 + (K_{I_3^-}/[I^-]))(-d[I_3^-]/dt) \qquad (5)$$

tration is effectively constant throughout the reaction and since the slope of the zero-order plot ($-dA/dt$) is directly related to $-d[I_3^-]/dt$ via the extinction coefficient of the triiodide ion, eq. 5 may be transformed into

$$k_1 = \{(K_{I_3^-} + [I^-])/(\epsilon_{I_3^-}[I^-][\text{ketone}])\}(-dA_{I_3^-}/dt) \qquad (6)$$

In reactions followed at the iodine–triiodide ion isosbestic point, or at the iodine absorption maximum, the rates of absorbance change were directly proportional to the enolization rates, and thus the term containing the triiodide dissociation constant was not required to evaluate k_1, as seen in eq. 7.

$$k_1 = (-dA/dt)/\epsilon[\text{ketone}] \qquad (7)$$

Experimental data for the iodination of o-isobutyrylbenzoic acid are listed in Table I. The precision of the first-order rate constants was limited by the combined uncertainties (5–6%) introduced into eq. 6 by the values of $\epsilon_{I_3^-}$ and $K_{I_3^-}$, and the concentration of iodide ion. The error involved in determination of the rates of absorbance change lowered the precision of the rate constants further (usually to 7–9%). The independence of the rate constants on the iodine concentration, shown by experiments 28 and 29, supports their identification as enolization rate constants.

The first-order rate constants of iodination are plotted against pH in Figure 1 (k vs. pH) and Figure 2 (log K vs. pH). The analysis of the pH dependence of the rate constants is considerably simplified by the fact that it is not necessary to consider intermolecular catalysis by general acids or bases. The data of Table I clearly show the absences of catalysis by external phthalate (experiments 2 and 3) and acetate (experiments 12–14) buffers, and the small concentrations of the keto acid employed exclude intermolecular autocatalysis. Catalysis by phosphate buffers may appear in experiments 24–26 and 30–32, but is of the same order of magnitude as the experimental errors, and the precision of the rate constants is not improved by taking the small buffer contribution into account.

Table I. Kinetics of Iodination of o-Isobutyrylbenzoic Acid[a]

Expt. no.	pH	$k_1 \times 10^7$ sec.$^{-1}$	Ketone $\times 10^4$, M	Buffer,[b] M		I_2[c] $\times 10^4$ M	NaI $\times 10^2$ M
1	0	13.1 ± 1.1	98.5	H	1.19	0.50	0.0
2	2.53	1.57 ± 0.42	9.27	T	0.040	0.83	0.50
3	2.84	3.85 ± 0.37	14.1	T	0.0050	0.83	0.50
4	2.88	3.41 ± 0.56	7.04	T	0.040	0.83	0.50
5	3.34	5.03 ± 0.58	3.20	T	0.040	0.33	5.0
6	3.58	7.33 ± 0.72	3.20	A	0.10	0.33	5.0
7	3.70	8.4 ± 1.1	3.20	A	0.10	0.33	5.0
8	3.89	12.6 ± 1.1	3.20	A	0.10	0.33	5.0
9	3.99	15.0 ± 2.1	3.20	A	0.10	0.33	5.0
10	4.10	17.6 ± 1.4	3.20	A	0.10	0.33	5.0
11	4.31	25.7 ± 2.2	3.20	A	0.10	0.33	5.0
12	4.55	32.6 ± 5.2	3.09	A	0.10	0.33	5.0
13	4.56	33.6 ± 2.5	3.09	A	0.010	0.33	5.0
14	4.59	33.7 ± 3.9	3.09	A	0.60	0.33	5.0
15	4.92	38.4 ± 2.7	3.20	A	0.10	0.33	5.0
16	5.41	43.2 ± 3.3	3.20	A	0.10	0.33	5.0
17	5.51	46.4 ± 3.9	3.52	P	0.16	0.33	5.0
18	5.52	45.6 ± 3.0	3.20	A	0.10	0.33	5.0
19	5.52	45.9 ± 3.4	3.09	P	0.16	0.33	5.0
20	5.71	48.4 ± 3.8	3.09	P	0.16	0.33	5.0
21	5.73	46.2 ± 3.2	3.52	P	0.16	0.33	5.0
22	5.76	45.0 ± 4.2	3.20	P	0.0080	0.33	5.0
23	5.89	49.4 ± 3.2	3.52	P	0.16	0.33	5.0
24	6.16	46.3 ± 3.3	3.20	P	0.010	0.33	5.0
25	6.20	50.9 ± 3.6	3.20	P	0.10	0.33	5.0
26	6.22	51.8 ± 3.6	3.20	P	0.20	0.33	5.0
27	6.80	50.0 ± 3.8	3.09	P	0.10	0.33	5.0
28	6.81	46.8 ± 3.0	32.0	P	0.10	0.33	5.0
29	6.81	47.0 ± 2.2[d]	96.0	P	0.10	10	5.5
30	6.89	47.4 ± 3.3	3.20	P	0.0080	0.33	5.0
31	6.89	47.9 ± 3.4	3.20	P	0.032	0.33	5.0
32	6.90	53.5 ± 3.9	3.20	P	0.20	0.33	5.0
33	7.02	48.8 ± 2.9	3.20	P	0.16	0.33	0.50
34	7.02	51.4 ± 3.6	3.20	P	0.16	0.33	5.0
35	7.80	52.4 ± 3.3	3.52	P	0.16	0.33	5.0
36	8.77	52.5 ± 3.7	3.20	C	0.010	0.33	5.0
37	9.54	56.0 ± 3.6	3.20	C	0.010	0.33	5.0
38	10.21	62.3 ± 4.8	32.0	P	0.010	0.33	5.0
39	10.24	64.0 ± 4.4	3.20	P	0.010	0.33	5.0
40	10.84	84.8 ± 6.9	32.0	P	0.010	0.33	5.0

[a] 25.0 ± 0.1°, ionic strength 0.50 ± 0.01. [b] T, phthalate; A, acetate; P, phosphate; C, carbonate. [c] Initial concentration of total iodine (iodine plus triiodide ion). [d] Measured at 470.0 mμ.

The absence of significant buffer catalysis, coupled with the sigmoid curve of Figure 1, suggests that the iodination reaction depends on the o-carboxylic acid group of the substrate. This carboxylic acid group has a pK_a of 4.23 ± 0.22 (μ = 0.5) and may be expected to catalyze the enolization reaction necessary for iodination either in its protonated or ionized form. The sigmoid curve of Figure 1 indicates that the carboxylate ion is more efficient as an internal catalyst than is the carboxylic acid, but even the latter does not appear to be negligible. The pH dependence of the iodination rate constant may be written as

$$k_1 = \frac{k_A}{1 + ([H^+]/K_a)} + \frac{k_{AH}}{1 + (K_a/[H^+])} \qquad (8)$$

where k_A is the rate constant of the anionic form of the keto acid, k_{AH} is the rate constant of the protonated form of the keto acid, and K_a is the ionization constant of the keto acid. The mean of the first-order rate constants of the pH-independent region between pH 6.5 and 9 gives directly the catalytic constant of the o-isobutyrylbenzoate anion, k_A = 4.98 ± 0.33 × 10^{-6} sec.$^{-1}$. The value of the ionization constant of the catalytic group involved in the iodination reaction may

be determined from a plot of the data according to eq. 9, which is a rearranged form of eq. 8. Such a

$$k_1 = K_a(k_A - k_1)/[H^+] + k_{AH} \qquad (9)$$
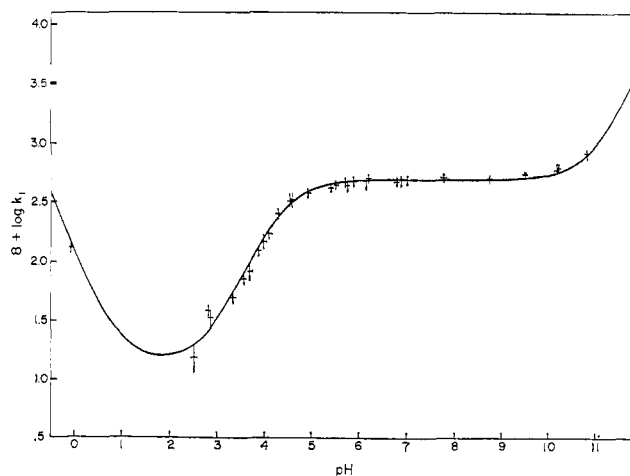
plot is shown in Figure 3, utilizing the data from pH

Figure 2. The kinetics of iodination of o-isobutyrylbenzoic acid at 25.0° in aqueous solution, μ = 0.50. The curve is a calculated curve using eq. 11 and the rate constants listed in the text.
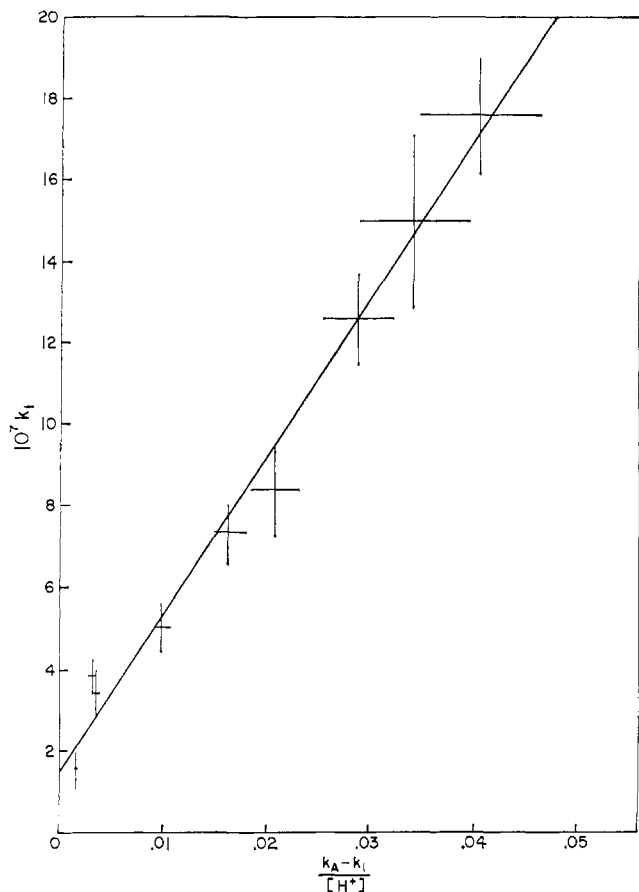
Figure 3. A plot of eq. 9 for the iodination of o-isobutyrylbenzoic acid at 25.0° in aqueous solution, $\mu = 0.50$, from pH 2.5 to 5.0.

2.5 to 5.0. The slope of this plot yields a kinetically determined ionization constant of $pK_a = 4.41 \pm 0.02$ which compares favorably with the spectrophotometrically measured ionization constant of the keto acid ($pK_a = 4.23 \pm 0.22$). The intercept of this plot gives $k_{AH} = 1.5 \pm 0.4 \times 10^{-7}$ sec.$^{-1}$. The data at low pH also yield a value for k_A, by using eq. 10, another

$$k_1\left(1 + \frac{K_a}{[H^+]}\right) = k_A \frac{K_a}{[H^+]} + k_{AH} \qquad (10)$$

variant of eq. 8. From a plot of eq. 10, it is found that $k_A = 5.08 \pm 0.19 \times 10^{-6}$ sec.$^{-1}$, in agreement with the mean of the pH-independent rate constants determined directly, and $k_{AH} = 1.2 \pm 0.2 \times 10^{-7}$ sec.$^{-1}$.

The three rate constants obtained above pH 9 were plotted against the hydroxide ion concentration, giving a catalytic constant for the hydroxide ion catalyzed reaction, $k_{OH} = 4.4 \pm 1.6 \times 10^{-3}$ M^{-1} sec.$^{-1}$. A single experiment at pH 0 (1.19 M perchloric acid) gave a catalytic constant for the hydrogen ion catalyzed reaction, $k_H = 1.10 \pm 0.10 \times 10^{-6}$ M^{-1} sec.$^{-1}$. These rate constants are, of course, of only limited accuracy.

The smooth curves shown in Figures 1 and 2 are calculated curves drawn using the various catalytic rate constants listed here, together with eq. 11, which extends eq. 8 to include the highly acidic and highly basic regions.

$$k_1 = k_H[H^+] + \frac{k_{AH}}{1 + (K_a/[H^+])} + \frac{k_A}{1 + ([H^+]/K_a)} + k_{OH}[OH^-] \qquad (11)$$

Discussion

The major reaction in the iodination of o-isobutyrylbenzoic acid consists of the region from pH 2.5 to 10. In this region, the reaction apparently is dependent solely on the anionic form of the substrate and is independent of external buffer catalysts and external hydronium ion and hydroxide ion. However, the reaction in this region may be kinetically described either as a reaction of o-isobutyrylbenzoate ion or as a reaction of isobutyrylbenzoic acid with hydroxide ion.

The kinetic descriptions of the major enolization reaction have their mechanistic counterparts. The enolization of o-isobutyrylbenzoate ion may be described as an intramolecular carboxylate ion catalysis as shown in eq. 12. The enolization of o-isobutyrylbenzoic acid with hydroxide ion may be described as an intramolecular carboxylic acid catalysis of a hydroxide ion reaction, as shown in eq. 13. Equation 13 indicates the lactol-keto acid equilibrium of o-isobutyrylbenzoic acid, in which the cyclic form predominates almost completely, as pointed out earlier.

Arguments are presented here which eliminate eq. 13 and thus indicate that eq. 12 describes the major enolization reaction of o-isobutyrylbenzoate ion.

(12)
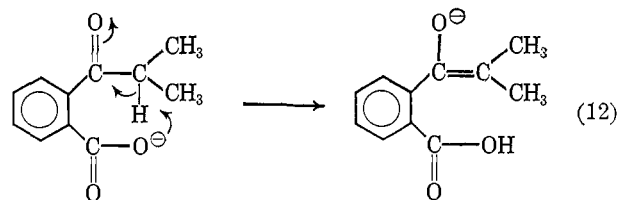
If mechanisms 13 involving hydroxide ion were operative, the catalytic constant k_A would be a complex constant, equal to $k_{OH}*K_w/K_a$, where $k_{OH}*$ is the bimolecular rate constant for hydroxide ion in either of eq. 13, K_w is the ion product of water, and K_a is the

(13)
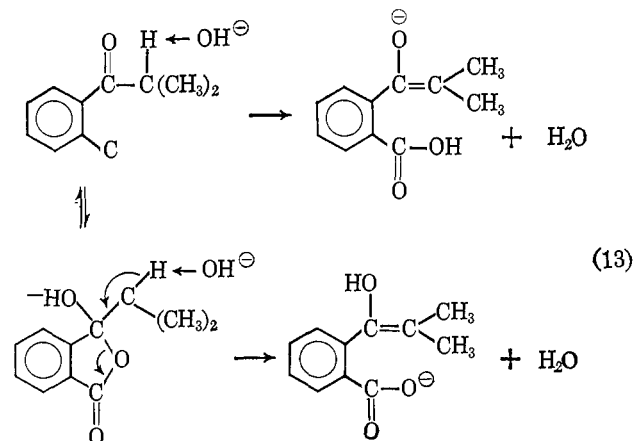
ionization constant of the keto acid. Using the known values of the various constants, $k_{OH}*$ may be calculated to be 25,000 M^{-1} sec.$^{-1}$. However, since the concentration of the keto acid form is negligibly small (with respect to the lactol form), the rate constant for its reaction via eq. 13 would be close to diffusion controlled, and thus reaction through the keto acid form of eq. 13 is highly improbable.

Furthermore, reaction through neither the lactol form nor the keto acid form of eq. 13 can explain experiments with o-acetylbenzoate ion which indicate that this com-

pound is halogenated at a *slower* rate than *o*-isobutyryl-benzoate ion. This result is to be compared with the intermolecular general base catalyzed iodination of acetophenone and isobutyrophenone, and of acetone and diisopropyl ketone; in these reactions the methyl ketone is always iodinated faster than the isopropyl ketone.[33,34] This reversal of substituent effect in the iodination of the keto acids is difficult to explain on the basis of eq. 13, but may be explained in two ways in terms of eq. 12, the intramolecular general basic process.

The retarding influence of α-alkyl groups on the rates of base-catalyzed enolization of ketones is generally explained as an inductive effect.[35] If one invokes the inductive basis of the substituent effects in intermolecular enolization, it is possible to invoke a special steric effect to explain the reversal of the substituent effects in an intramolecular catalysis. Part of the entropy of activation in an enolization stems from the loss of rotational freedom of the alkyl group in the transition state. Models suggest that, while in the *o*-acetylbenzoate ion ground state the methyl group may rotate freely, the isopropyl group in the *o*-isobutyryl-benzoate ion ground state probably cannot rotate at all, because of steric interference between the carboxylate group and the isopropyl group. The preferred conformation of the *o*-isobutyrylbenzoate ion ground state will be one which is relatively rigid and one in which the lone α-hydrogen is directly adjacent to the *o*-carboxylate ion. Thus the enolization of *o*-isobutyrylbenzoate ion will be sterically assisted, compared to the enolization of the *o*-acetylbenzoate ion. The magnitude of this steric assistance can be calculated, assuming a value of 5 cal./deg. mole for the entropy of rotation about a single bond.[36] On the basis that the acetyl compound loses the entropy associated with rotation about one single bond in the activation process while the isobutyryl compound does not, it may be calculated that the isobutyryl-benzoate ion enolization should proceed faster than the *o*-acetylbenzoate enolization by a factor of 13. This effect is opposed by an inductive effect of 10 in the opposite direction,[33,34] leading to the conclusion that the isobutyrylbenzoate enolization should be slightly faster than the acetylbenzoate enolization, a result consistent with our preliminary results.

The retarding influence of α-alkyl groups on the rates of base-catalyzed enolization of ketones may alternatively be interpreted in terms of steric retardation of proton transfer. Rate retardations of up to 50-fold have been established in general base catalyzed reactions.[37] If the alkyl substituent effect represents steric hindrance in intermolecular general basic catalysis, it might be expected that the effect would be overcome in intramolecular general basic catalysis in *o*-acylbenzoate ions. For example, the higher energy

and more negative entropy of activation in the intermolecular reaction would be compensated by the higher energy and lower entropy of the starting material in the intramolecular reaction.

The significance of the intramolecular general basic catalysis may be determined by comparison of its catalytic rate constant (5×10^{-6} sec.$^{-1}$) to that for the corresponding intermolecular general basic catalysis, the iodination of isobutyrophenone with benzoate ion as catalyst. The rate constant for this reaction can be estimated from the known rate constant of the iodination of acetophenone using acetate ion as catalyst. The rate constant of the latter reaction is $\sim 8 \times 10^{-7}$ M^{-1} sec.$^{-1}$.[38] The rate constant of the former reaction is $^1/_{10}$ of this rate constant on the basis that the reactivity of isobutyrophenone is $^1/_3$ that of acetophenone[33,34] (a statistical correction for the difference in the number of hydrogen atoms has been made), and the reactivity of benzoate ion is $^1/_3$ that of acetate ion in enolization reactions.[4] The calculated rate constant for the reaction of benzoate ion with isobutyrophenone is thus approximately 3×10^{-8} M^{-1} sec.$^{-1}$. Experiments on the benzoate ion catalyzed deuterium exchange of isobutyrophenone at 66 and 100°, when extrapolated to 25°, give an enolization rate constant of this order of magnitude.[39] The intramolecular general basic catalysis in the iodination of *o*-isobutyrylbenzoate ion and the intermolecular general catalysis in the iodination of isobutyrophenone catalyzed by benzoate ion may be compared by determining the magnitude of the concentration of intermolecular catalyst required to make the rate of the latter process equal the rate of the former process.[40] From the calculation given above, this quantity is 56 M benzoate ion, implying that 56 M benzoate ion would be necessary for the rate of the intermolecular process to equal that of the intramolecular process. Because of the approximations involed, this comparison is probably good only to a factor of 2. In contrast, the rate enhancement of intramolecular general basic catalysis of the most efficient levulinic acid homolog, 5-ketohexanoic acid, over intermolecular general basic autocatalysis in levulinic acid enolization corresponds to 1 M levulinate ion.[12]

If general base catalyzed enolization of simple ketones proceeds *via* rate-determining proton abstraction by a base, and if general acid catalyzed enolization of ketones involves reaction of the protonated ketone with the conjugate base of the acid,[41] the mechanism of catalysis by the undissociated *o*-carboxylic acid must involve intramolecular catalysis in the zwitterionic form of the keto acid as in eq. 14. This description of the

$$(14)$$
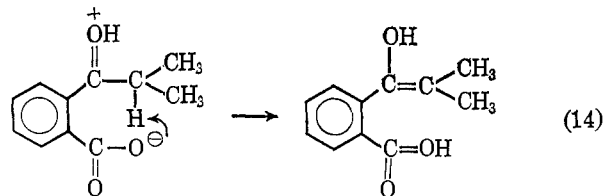
(33) C. F. Cullis and M. H. Hashmi, *J. Chem. Soc.*, 1548 (1957); acetone *vs.* diisopropylketone.

(34) D. P. Evans and J. J. Gordon, *ibid.*, 1434 (1938); acetophenone *vs.* isobutyrophenone.

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(36) H. A. Scheraga, "Protein Structure," Academic Press Inc., New York, N. Y., 1961, p. 40; E. G. Foster, A. C. Cope, and F. Daniels, *J. Am. Chem. Soc.*, 69, 1893 (1947); P. D. Bartlett and R. R. Hiatt, *ibid.*, 80, 1402 (1958).

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(38) E. T. Harper, unpublished experiments.

(39) E. T. Harper and G. C. Tsuei, unpublished experiments.

(40) M. L. Bender, *Chem. Rev.*, 60, 88 (1960).

(41) C. G. Swain, A. J. Di Milo, and J. P. Cordner, *J. Am. Chem. Soc.*, 80, 5983 (1958); C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *ibid.*, 80, 5885 (1958); C. G. Swain and A. S. Rosenberg, *ibid.*, 83, 2154 (1961).

mechanism of enolization of protonated o-isobutyryl-benzoic acid is complicated by the fact that it exists predominantly in the lactol form as shown in eq. 13, leading to the possibility of a catalysis of the un-ionized lactol form by water. However, catalysis of the un-ionized form of the substrate by water is excluded by the absence of (more powerful) buffer catalysis.

The catalytic constant k_{OH} for the iodination of o-isobutyrylbenzoate ion represents intermolecular hydroxide ion attack on this anion. A comparison of the rate constant of this reaction with the hydroxide ion catalyzed iodination of isobutyrophenone (calculated as discussed previously) shows that the former reaction is about 20 times slower than the latter reaction. The difference can of course be attributed to electrostatic repulsion of the hydroxide ion by the o-carboxylate ion in the former reaction.

Several mechanisms can be written for the hydronium ion catalyzed enolization, measured in 1 M perchloric acid. These mechanisms involving the protonated ketone or the protonated lactol cannot be differentiated at the present time.

The demonstration of a powerful intramolecular general basic catalysis of ketone enolization in o-isobutyrylbenzoate ion may serve as a model for the enolization of dihydroxyacetone phosphate by a general base of the enzyme aldolase in the enzyme–substrate complex formed between these two substances. Certainly there are more efficient bases on the enzyme than the carboxylate ion investigated here. However, the present experiments do show the possibility that a considerable portion of the rate enhancement in enzymatic enolization processes may involve intramolecular or intracomplex general basic catalysis.

# Stable Carbonium Ions. XVIII.[1a] Alkynyl Carbonium Ions

Charles U. Pittman, Jr., and George A. Olah[1b]

Contribution from the Eastern Research Laboratory, The Dow Chemical Company, Wayland, Massachusetts. Received August 16, 1965

Using the previously reported method of ionizing alcohols in fluorosulfonic acid–antimony pentafluoride–sulfur dioxide solvent system, seven alkynyl carbonium ions were directly observed by nuclear magnetic resonance spectroscopy. The spectra indicate that allenyl cation forms are strong contributors in alkynyl carbonium ions.

Introduction

The only previous reported observation of alkynyl carbonium ions was that of Richey, Philips, and Rennick who observed ions I and II in concentrated sulfuric acid solution by n.m.r. and ultraviolet spectroscopy.[2] In their investigations they also reported
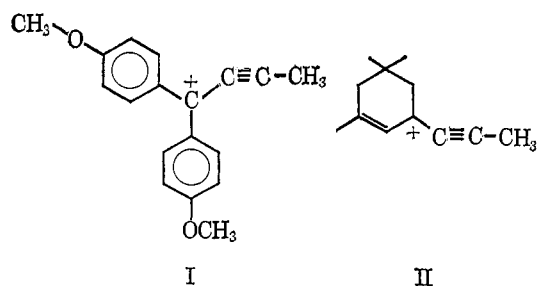
recovery of the precursor alcohols by drowning the sulfuric acid solutions with excess sodium hydroxide.

Results and Discussion

Continuing our systematic investigation of different classes of stable carbonium ions[3] we wish now to report the direct observation of a series of alkynyl carbonium ions by n.m.r. spectroscopy.[4]

Using the analogy of the alkyl halide–antimony pentafluoride method to generate stable carbonium ions, an attempt was made to generate stable alkynyl carbonium ions from $(CH_3)_2C(Cl)C\equiv CH$ and $(CH_3)_2C(Cl)$—$C\equiv CCH_3$.[5] In neat antimony pentafluoride and also in antimony pentafluoride–sulfur dioxide the spectra obtained were of poor quality and showed extensive by-product formation.

Some time ago Olah, *et al.*, reported[6] that tertiary alcohols ionize well to the corresponding stable carbonium ions in fluorosulfonic acid–antimony pentafluoride–sulfur dioxide. Using this method, it was found that tertiary alkynyl alcohols ionize to stable alkynyl carbonium ions.

Alkynyl carbonium ions were generated by dissolving the corresponding alkynyl alcohols into liquid SO_2 at $\sim -50°$ and adding this solution to a rapidly stirring solution of SbF_5–FSO_3H–SO_2 at $\sim -70°$. The n.m.r. spectra of ions III–IX are shown in Figures 1–7, respectively (recorded at $\sim -60°$). The

(1) (a) Part XVII: C. U. Pittman, Jr., and G. A. Olah, *J. Am. Chem. Soc.*, **87**, 5123 (1965); (b) to whom inquiries should be addressed at the Department of Chemistry, Western Reserve University, Cleveland, Ohio.

(2) H. G. Richey, J. C. Philips, and L. E. Rennick, Jr., *J. Am. Chem. Soc.*, **87**, 1381 (1965).

(3) G. A. Olah, *et al.*, *ibid.*, **84**, 2733 (1962); **85**, 1328 (1963); **86**, 1932, 1265, 1360, 4195, 5679, 5680, 5682 (1964); **87**, 1103, 2997, 2998 (1965).

(4) After our work was completed, we learned of independent work of Professor Richey and his co-workers. We are grateful for preprints of this work.

(5) We are grateful to Professor T. Jacobs, University of California, Los Angeles, for samples of the alkynyl chlorides.

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