Evidence for the Formation of Two Tetrasubstituted Intermediates in the Alkaline Hydrolysis of Ethyl Thionbenzoate[1a]

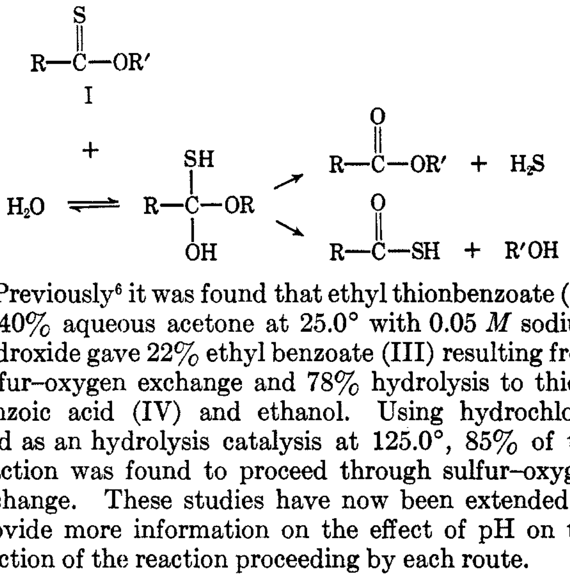
STANLEY G. SMITH[1b] AND RAYMOND J. FELDT

The Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois 61801

Received September 15, 1967

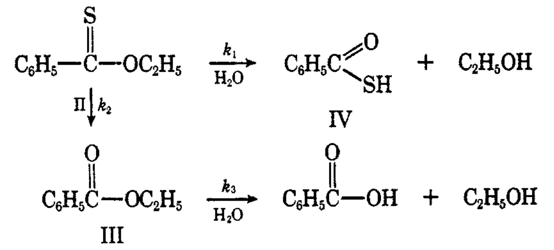
The effect of pH on the rate and the yield of ethyl benzoate and thiobenzoic acid in the hydrolysis of ethyl thionbenzoate in 50% aqueous dioxane has been studied. Over the pH range of 4–12 the product of hydrolysis is very largely ethyl benzoate arising from sulfur–oxygen exchange. Under more alkaline conditions the fraction of the reaction giving ethyl benzoate drops to 0.4 with thiobenzoic acid becoming the major product. The change in the course of the reaction with acidity may be accounted for by a pH-dependent equilibrium between at least two intermediates.

Tetrasubstituted[2] intermediates in the reaction of nucleophiles with carboxylic esters have generally been invoked to explain ^{18}O exchange,[3] spectral,[4] and kinetic data.[3,5] Thion esters,[6] I, constitute a particularly instructive system for the study of such intermediates since in aqueous medium the process which formally corresponds to oxygen exchange with carboxylic esters gives rise to sulfur–oxygen exchange and the formation of the corresponding oxo ester (eq 1).



$$\underset{\text{I}}{R-\overset{S}{\overset{\|}{C}}-OR'} + H_2O \rightleftharpoons R-\underset{OH}{\underset{|}{\overset{SH}{\overset{|}{C}}}}-OR \begin{array}{l} \nearrow R-\overset{O}{\overset{\|}{C}}-OR' + H_2S \\ \searrow R-\overset{O}{\overset{\|}{C}}-SH + R'OH \end{array} \quad (1)$$

Previously[6] it was found that ethyl thionbenzoate (II) in 40% aqueous acetone at 25.0° with 0.05 M sodium hydroxide gave 22% ethyl benzoate (III) resulting from sulfur–oxygen exchange and 78% hydrolysis to thionbenzoic acid (IV) and ethanol. Using hydrochloric acid as an hydrolysis catalysis at 125.0°, 85% of the reaction was found to proceed through sulfur–oxygen exchange. These studies have now been extended to provide more information on the effect of pH on the fraction of the reaction proceeding by each route.



Results and Discussion

Reaction Conditions.—The hydrolysis of ethyl thionbenzoate (II) was studied in 50% aqueous dioxane at an apparent pH of 1.5 to 15.3 and temperatures varying from 25.0 to 125.0°. The low pH region was obtained with 0.02 to 0.05 M p-toluenesulfonic acid while sodium hydroxide solutions, 0.002 to 0.5 M, were used in the alkaline region. Intermediate acidities, pH 4.5 to 10.8, were obtained with 2,6-lutidine–p-toluenesulfonic acid or diisopropylethylamine–p-toluenesulfonic acid buffers. The pH was measured with a glass electrode and calomel reference with 10^{-3} M hydrochloric acid in 50% aqueous dioxane being used to define a pH of three. Above a pH of 10.7 erratic pH measurements were obtained so an indicator overlap method[7] was employed to extend the pH values (see Experimental Section).

Kinetics.—The rate constants for the disappearance of ethyl thionbenzoate ($k_1 + k_2$) were obtained by a spectrophotometric analysis at 414 mμ or of extracted aliquots at 290 mμ. A typical run is given in Table I.

TABLE I

HYDROLYSIS OF 0.0107 M ETHYL THIONBENZOATE IN A DIISOPROPYLETHYLAMINE–p-TOLUENESULFONIC ACID BUFFER OF pH 10.7 IN 50% AQUEOUS DIOXANE AT 125.0° FOLLOWED BY ABSORBANCE AT 290 mμ

Time, 10^{-4} sec	Absorbance, mμ	$10^5(k_1 + k_2)$, sec^{-1}
0	0.995	
0.45	0.876	2.84
0.96	0.771	2.67
1.29	0.701	2.73
1.59	0.662	2.58
1.89	0.603	2.66
2.25	0.550	2.65
2.61	0.497	2.68
3.04	0.453	2.61
3.42	0.409	2.62
3.87	0.369	2.58
51.20	0.004	
	Least squares	2.60

Rate constants determined in 2,6-lutidine–p-toluenesulfonic acid buffers were found to be essentially independent of the buffer concentration employed (Table II), but measurements made in diisopropylethylamine–p-toluenesulfonic acid buffers had to be extrapolated to zero buffer concentration (Figure 1). Second-order rate constants observed in runs with added sodium hydroxide are summarized in Table III. The pseudo-

---

(1) (a) Research supported by the National Science Foundation; (b) Alfred P. Sloan Fellow.

(2) Intermediates in ester hydrolysis are often described as tetrahedral; however, the molecular asymmetry makes it unlikely that they actually conform to tetrahedral geometry.

(3) (a) D. Samuel and B. L. Silver in "Advances in Physical Organic Chemistry," Vol. 3, V. Gold, Ed., Academic Press Inc., New York, N. Y., 1965, p 123; (b) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (c) M. L. Bender and H. d'A. Heck, *J. Amer. Chem. Soc.*, **89**, 1211 (1967); (d) M. L. Bender and R. J. Thomas, *ibid.*, **83**, 4189 (1961); (e) M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *ibid.*, **83**, 4193 (1961).

(4) (a) M. L. Bender, *ibid.*, **75**, 5986 (1953); (b) Y. Hirshberg, D. Lavie, and E. D. Bergmann, *J. Chem. Soc.*, 1030 (1951).

(5) *E.g.*, (a) L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.*, **87**, 4138 (1965); (b) S. L. Johnson, *ibid.*, **86**, 3819 (1964); (c) G. E. Lienhard and W. P. Jencks, *ibid.*, **87**, 3855 (1965); (d) L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 4117 (1964); (e) T. C. Bruice and L. R. Fedor, *ibid.*, **86**, 4886 (1964).

(6) S. G. Smith and M. O'Leary, *J. Org. Chem.*, **28**, 2825 (1963).

(7) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y. 1940, p 252.

TABLE II

SUMMARY OF THE FIRST-ORDER RATE CONSTANTS FOR THE DISAPPEARANCE OF ETHYL THIONBENZOATE IN 50% AQUEOUS DIOXANE AT 125.0°

pH[a]	Added reagents: HOTs,[b] 10^2M	Added reagents: Amine, 10^2M	NaOH, 10^2M	Ethyl thionbenzoate, 10^2M	10^5k_{obsd}, sec^{-1}	10^5k_1, sec^{-1}	10^5k_2, sec^{-1}	$k_1/(k_1+k_2)$
1.45	4.96			1.1	1.52	0.16	1.36	0.10
1.95	1.93			1.2	0.842	0.11	0.831	0.13
4.5	8.18	8.69[c]		1.2	0.392	0	0.41	0
5.6	2.43	4.41[c]		0.92	0.40			
5.6	4.90	8.54[c]		1.02	0.419	0.003	0.416	0
5.6		*d*		0.97	0.375			
6.3	0.70	4.41[c]		0.97	0.404			
6.3	1.28	8.50[c]		1.11	0.427	0.003	0.424	0
6.3		*d*		1.40	0.375			
7.0	0.15	4.40[c]		1.23	0.406			
7.0	0.31	8.70[c]		0.88	0.427	0.046	0.381	0.11
7.0		*d*		1.09	0.375			
9.4	5.09	5.58[e]		1.04	0.493			
9.4	8.52	9.22[e]		1.05	0.523	0	0.606	0
9.4		*d*		1.05	0.456			
10.3	2.42	4.39[e]		1.11	1.11			
10.3	4.09	7.35[e]		1.05	1.35			
10.3	5.08	9.16[e]		1.09	1.55	0	1.62	0
10.3		*d*		1.08	0.680			
10.7	1.20	4.58[e]		1.03	1.94			
10.7	1.80	6.87[e]		1.08	2.29			
10.7	2.41	9.16[e]		1.07	2.60	0	2.86	0
10.7		*d*		1.08	1.29			
10.8[f]	0.81	4.59[e]		1.07	2.46	0	2.80	0
10.8[f]	1.22	6.87[e]		1.08	2.91			
10.8[f]	1.62	9.16[e]		1.02	3.30	0	3.48	0
10.8[f]		*d*		1.06	1.66	0	1.92	0
12.0[f]			0.175	0.087	738[h]	36.9[h]	743[h]	0.05
12.7[f]			0.35	0.130	1,030[h]	143[h]	847[h]	0.14
12.8[f]			0.55	0.125	1,900[h]	730[h]	1,100[h]	0.38
13.2[f]			1.12	0.128	5,600[h]	3,020[h]	2,600[h]	0.52
13.3[f]			1.55	0.75	4,600[h]	2,660[h]	2,000[h]	0.57
14.0[f]			3.06	0.99	12,500[h]	8,400[h]	3,400[h]	0.67
14.5[g]			10.5	1.27	33,000[h]	20,000[h]	12,000[h]	0.60
15.0[g]			31.7	1.20	70,000[h]	37,000[h]	31,000[h]	0.53
15.3[g]			50.0	1.05	72,000[h]	43,000[h]	28,000[h]	0.59

[a] Apparent pH determined at 25° in 50% aqueous dioxane with glass electrode–calomel reference electrode. [b] *p*-Toluenesulfonic acid. [c] 2,6-Lutidine. [d] Extrapolated to zero buffer concentration. [e] Diisopropylethylamine. [f] Determined with indicators. [g] Estimated from a plot of apparent pH *vs.* log (NaOH). [h] Rate constants in the presence of sodium hydroxide calculated from data at 25.0 and 50.1°.

TABLE III

SUMMARY OF SECOND-ORDER RATE CONSTANTS FOR THE DISAPPEARANCE OF ETHYL THIONBENZOATE, k_{obsd}, THE APPEARANCE OF ETHYL BENZOATE, k_2, AND THE APPEARANCE OF THIOBENZOIC ACID, k_1, IN THE PRESENCE OF SODIUM HYDROXIDE IN 50% AQUEOUS DIOXANE

pH[a]	Temp, °C	10^2[NaOH], M	Ethyl thionbenzoate, $10^2\ M$	10^3k_{obsd}, M^{-1} sec^{-1}	10^3k_1, M^{-1} sec^{-1}	10^3k_2, M^{-1} sec^{-1}	$k_1/(k_1+k_2)$
12.0	50.0	0.175	0.0866	43.2	2.8	40.6	0.065
12.7	25.0	0.325	0.132	5.80	2.34	3.46	0.40
12.7	50.0	0.381	0.127	39.4	13.6	25.8	0.35
12.8	25.0	0.588	0.125	5.23	2.29	2.94	0.44
12.8	50.0	0.540	0.118	39.3	16.7	22.6	0.42
13.2	25.0	1.12	0.128	5.01	2.64	2.38	0.53
13.2	50.0	1.09	0.128	41.8	22.2	19.6	0.53
13.3	25.0	1.56	0.69	5.04	3.30	1.74	0.65
13.3	50.0	1.57	0.83	37.2	23.4	13.8	0.63
14.0	25.0	2.98	0.85	5.11	3.69	1.42	0.72
14.0	50.0	3.14	1.12	39.9	28.2	11.2	0.71
14.5[b]	25.0	10.5	1.27	4.29	2.92	1.37	0.68
15.0[b]	25.0	31.66	1.20	3.01	1.83	1.18	0.61
15.3[b]	25.0	50.4	1.07	1.96	1.26	0.70	0.64

[a] Apparent pH determined by indicator method. [b] Estimated from a plot of apparent pH *vs.* log (NaOH).

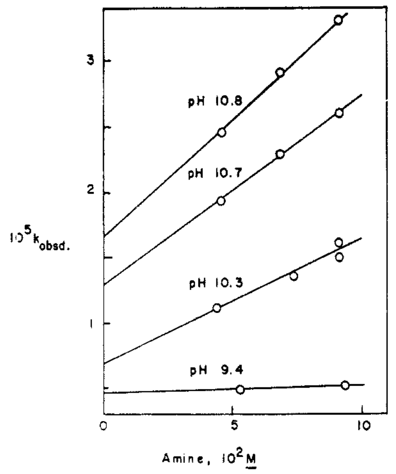


Figure 1.—Plot of first-order rate constants for the disappearance of ethyl thionbenzoate in 50% aqueous dioxane at 125.0° as a function of the concentration of diisopropylethylamine in amine–*p*-toluenesulfonic acid buffers.

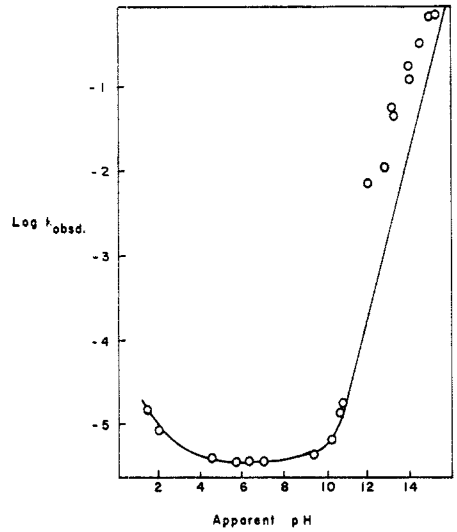


Figure 2.—Plot of log k_{obsd} for the disappearance of ethyl thionbenzoate in aqueous dioxane at 125.0° *vs.* pH.

first-order rate constant, k_{obsd}, for the acidic and buffered runs as well as the second-order rate constants divided by the initial base concentration obtained in the runs with added sodium hydroxide were all corrected, where necessary, to the same temperature of 125.0°, and extrapolated to zero buffer concentration are summarized in Table II and displayed in Figure 2.

The kinetic data are represented reasonably well by eq 3 from a pH of 1.5–10.8, the line in Figure 2 being calculated with the indicated parameters. Deviation of experimental data from eq 3 under more alkaline

$$k_{obsd} = 3.1 \times 10^{-4}a_{H^+} + 3.8 \times 10^{-6} + \frac{1.8 \times 10^{-16}}{a_{H^+}} \quad (3)$$

conditions is most likely due to the long extrapolation required to represent the data at a single temperature as well as inadequate control of ionic strength. It is clear, however, that uncatalyzed water hydrolysis is the predominate reaction in neutral solution with substantial acid catalysis below a pH of *ca.* 3. Direct hydroxide participation is apparent above a pH of *ca.* 10.

The presence of the oxygen exchanged product, ethyl benzoate, was detected in aliquots taken during the reaction by an analysis of the uv absorbance at both 230 and 290 mμ in runs containing sodium hydroxide and by glpc analysis under all other conditions. A sample run is illustrated in Table IV and Figure 3.

Table IV

Hydrolysis of 0.0089 *M* Ethyl Thionbenzoate in the Presence of 0.0158 *M* Sodium Hydroxide in 50% Aqueous Dioxane at 50.0° by Absorbance at 230 and at 290 mμ

Time, 10^{-3} sec	Ethyl benzoate, 10^3 *M*	Ethyl thion-benzoate, 10^3 *M*	10^2k_2, M^{-1} sec^{-1}	$10^2(k_1 + k_2)$, M^{-1} sec^{-1}
0	0.325	8.175		
0.265	0.646	7.050	1.42	3.87
0.538	0.849	6.219	1.35	3.64
0.838	1.030	5.336	1.31	3.79
1.125	1.115	4.758	1.33	3.68
1.410	1.223	4.179	1.30	3.75
1.696	1.314	3.738	1.34	3.73
1.990	1.323	3.338	1.32	3.73
2.292	1.360	3.002	1.34	3.71
2.601	1.399	2.718	1.38	3.66
2.913	1.375	2.455	1.36	3.65
		Av	1.38 ± 0.07	Least squares 3.72 ± 0.02

It has been shown previously that the rate constant, k_2, of eq 2 may be calculated from the concentration at any time of ethyl benzoate, [O], the thion ester, [S], the initial thion ester concentration, $[S]_0$, and k_3 by using eq 4.

$$k_2 = \frac{([O]/[S])(k\ + k_2 - k_3)}{-1 + ([S]^{(k_3-k-k_2)/(k_1+k_2)}/[S_0])} \quad (4)$$

The values of k_3 were obtained from separate experiments using ethyl benzoate as the substrate. These values are tabulated in Tables V and VI. It is of interest to note that under acidic, pH < 2, and alkaline, pH > 10, reaction conditions ethyl benzoate hydrolyses at a rate comparable with that of ethyl thionbenzoate. However, in the intermediate, neutral region the thion ester is much more reactive toward hydrolysis. At a pH of 7, for example, at 125°, ethyl thionbenzoate hydrolysis is faster than ethyl benzoate by a factor of *ca.* 10^3.

Table V

Summary of First-Order Rate Constants for the Hydrolysis of Ethyl Benzoate at 125.0° in 50% Aqueous Dioxane

	Added reagents			
pH[a]	HOTs,[b] 10^2 *M*	Amine, 10^2 *M*	Ethyl benzoate, 10^2 *M*	10^5k_3, sec^{-1}
1.45	4.70		0.90	4.16
1.95	1.93		1.21	1.53
4.5	8.44	8.74[c]	1.09	0.0487
5.6	4.82	8.94[c]	1.14	0.00328
6.3	1.27	8.50[c]	1.07	0.0021
7.0	0.27	8.53[c]	1.03	0.0031
9.4	8.41	9.12[d]	1.07	0.0280
10.3	5.05	9.16[d]	0.54	0.318
10.7	2.42	9.22[d]	1.18	0.680
10.8	0.80	4.62[d]	1.22	0.636
10.8	1.62	9.16[d]	1.32	0.835

[a] Apparent pH determined with a glass electrode–calomel reference electrode. [b] *p*-Toluenesulfonic acid. [c] 2,6-Lutidine. [d] Diisopropylethylamine.

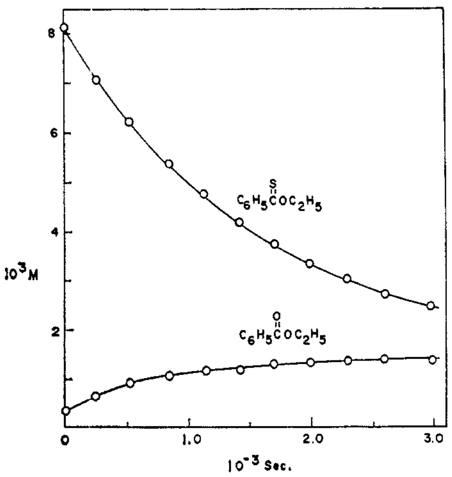


Figure 3.—Plot of concentration *vs.* time in the hydrolysis of 0.0089 *M* ethyl thionbenzoate in presence of 0.0158 *M* sodium hydroxide in 50% aqueous dioxane at 50.0°.

TABLE VI
SUMMARY OF SECOND-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF ETHYL BENZOATE IN THE PRESENCE OF SODIUM HYDROXIDE IN 50% AQUEOUS DIOXANE

pH[a]	Temp, °C	NaOH, 10^2 *M*	Ester, 10^2 *M*	10^3k_3, M^{-1} sec^{-1}
12.0	50.0	0.123	0.110	25.59
12.7	25.0	0.385	0.140	4.70
12.7	50.0	0.381	0.134	27.9
12.8	25.0	0.539	0.133	5.17
12.8	50.0	0.543	0.129	27.1
13.2	25.0	1.12	0.130	5.23
13.2	50.0	1.09	0.129	30.0
13.3	25.0	1.57	0.99	5.12
13.3	50.0	1.55	0.98	27.6
14.0	25.0	3.05	1.34	5.21
14.0	50.0	3.14	1.39	29.62
14.5[b]	25.0	10.70	1.33	5.14
15.0[b]	25.0	29.55	1.45	4.33
15.3[b]	25.0	51.7	0.91	3.09

[a] Apparent pH determined with indicators. [b] Estimated from a plot of apparent pH *vs.* log (NaOH).

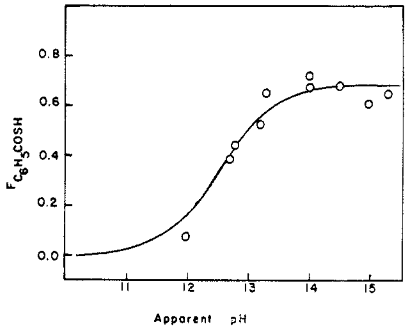
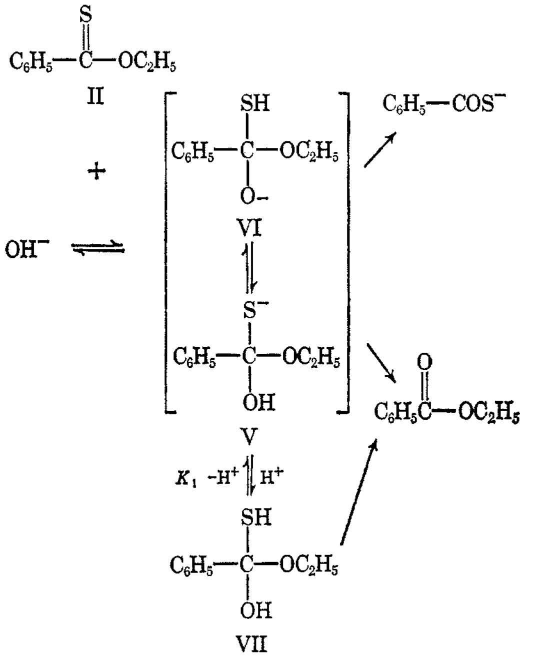


Figure 4.—Plot of fraction of thiobenzoic acid produced, $F_{C_6H_5COSH}$, *vs.* pH from the reaction of ethyl thionbenzoate in 50% aqueous dioxane containing various concentrations of sodium hydroxide. The line was calculated from eq 7 using a value of 10^{13} for k_4/K_5k_2.

From the summary of values of k_1 and k_2 given in Table II, it is apparent that the hydrolysis of ethyl thionbenzoate proceeds very predominately through ethyl benzoate from a pH of 4 to 11. Hydrolysis to thiobenzoic acid occurs to the extent of about 10% in 0.05 *M* toluenesulfonic acid solution. Under strongly alkaline conditions *ca.* 70% of the reaction results in formation of thiobenzoic acid (Table III) at 25°.

The dramatic change in the course of the reaction from essentially all sulfur–oxygen exchange to 68% of cleavage of the acyl–alkoxy bond with a change in pH from *ca.* 11 to 14 (Table III) is illustrated at the experimentally observed temperature of 25° in Figure 4. This change in initial products is not simply the result of a change to hydroxide as the attacking nucleophile since in the region from pH 9 to 12 the rate of hydrolysis increases by a factor of 10^3, reflecting the reactivity of hydroxide, yet the products do not change, only the sulfur–oxygen exchanged product, ethyl benzoate being observed. Apparently the acidity of the medium is more important than the nature of the nucleophile in determining the products. This is consistent with the formation of intermediates which are in acid–base equilibrium or at least exchange protons at a rate competitive with product formation.

A reaction scheme which should be considered for the conditions where the reaction is first order in the concentration of sodium hydroxide is given in eq 5



(5)

where the mercaptide anion V, alkoxide anion VI, and the neutral adduct VII all contribute to formation of products. The alkoxide, VI, is included since the mercaptide anion V would not be expected to give much sulfur–oxygen exchange. In the absence of anion VI, this would result in the fraction of the reaction yielding thiobenzoic acid approaching unity with increasing pH rather than the observed value of 0.68, assuming rapid proton transfers. The relative amounts of VI and V should, to a first approximation, be independent of pH.

The value of the equilibrium constant, K_1, is not known but may be approximated by using Kreevoy's[8] correlation of the pK_a's of mercaptans with structure.[9] The σ^* value[9] for $C_6H_5CH(OH)$- indicates that one hydroxyl group decreases the pK_a of benzyl mercaptan from 9.43 to 7.6. Assuming the σ^* value of a methoxyl

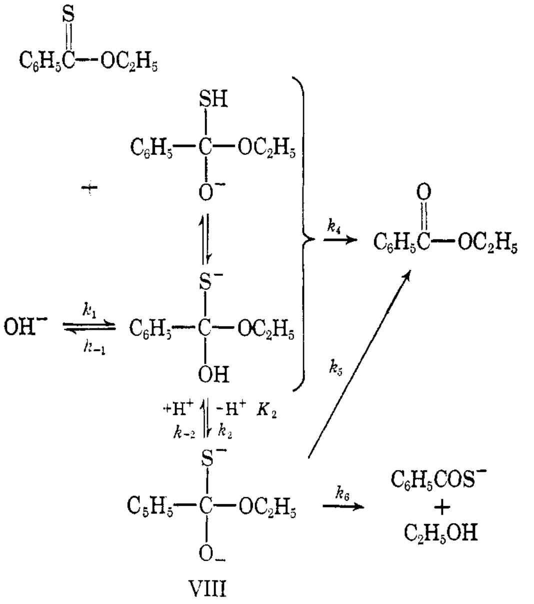
---

[8] M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, III, and L. T. Ditsch, *J. Amer. Chem. Soc.*, **82**, 4899 (1960).

[9] (a) R. W. Taft, Jr., *ibid.*, **74**, 2729 (1952); (b) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., 1956, Chapter 13.

group is the same as an ethoxyl group and group additivity gives an estimated pK_a in water of 5.8.

Even with a substantial medium effect[10] on the estimated pK_a for the solvent change from water to 50% aqueous dioxane (ΔpK_a of 1.9[10] for benzoic acid) the change in the course of the reaction with pH (Figure 4) occurs in a region (pH 12–14) where essentially all of the intermediate VII would have been converted into the corresponding pair of anions. This suggests that a much less acidic proton is responsible for the observed variation of product distribution with pH. Such a scheme is outlined in eq 6 in which the formation of the dianion VIII is depicted as the source of thiobenzoic acid.



(6)

The observed kinetics indicate that at high pH, for this scheme to be applicable, k_{-1} is small relative to $k_2(OH^-)$. The midpoint in the plot (Figure 4) corresponds to a pK_a of *ca.* 12.5 for formation of the dianion from the monoanion. On this base, the fraction of the reaction yielding thiobenzoic acid is given by eq 7. The

$$\text{Fraction } C_6H_5COS^- = \frac{k_6}{k_6 + k_5 + (k_4H^+/K_2)} = \frac{2.2}{3.2 + (k_4H^+/k_5K_2)} \quad (7)$$

limiting yield of thio acid at high base concentrations fixes the ratio of k_6/k_5 at 2.2. The line in Figure 4 describing the change in products with concentration of sodium hydroxide was calculated for a value of 10^{13} l./mol for k_4/k_5K_2. Using the estimated value for K_2 of 3×10^{-13} indicates that sulfide is lost from the dianion VIII three times faster than bisulfide and/or sulfide is lost from the monoanion.

Although it is possible to account for the over-all course of the reaction in alkaline solution with eq 6, it is possible that proton transfer is not fast relative to loss of sulfur or oxygen and equilibration of intermediates is not actually obtained. Bender[3d] has suggested such a mechanism to account for the effect of substituents on the hydrolysis and isotopic oxygen exchange of substituted methyl benzoates.

Experimental Section

Ethyl thionbenzoate was prepared from the corresponding imino ester by the method of Renson and Bidaine.[11]

Other Materials.—Commercially available ethyl benzoate (Eastman) and diisopropylethylamine (Aldrich) were distilled before use. Eastman *p*-toluenesulfonic acid monohydrate (25 g) was dissolved in 500 ml of ether and then precipitated by slowly adding an equal volume of cyclohexane. The product was filtered and dried in a vacuum desiccator.

The 2,6-lutidine (Eastman) was treated with boron trifluoride[12] and distilled twice before use, bp 141–143° (lit.[12] bp 143.4°).

Ethyl phenylacetate (Matheson) (*ca.* 50 g) was dissolved in 100 ml of cyclohexane, washed with two 30-ml portions of 7% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, concentrated, and distilled under reduced pressure, bp 62–62.5° (0.7 mm) (lit.[13] bp 100.5° (10 mm)). Gas chromatographic analysis on a 3.5-ft 20% XF-1150 on Chromsorb W column at 120° showed a small peak amounting to 0.6% of the area of the main peak. Since ethyl phenylacetate was used as the internal standard for quantitative gas chromatography and the small peak appeared under the ethyl thionbenzoate peak, a small correction was necessary in the thion ester peak area.

Solvent.—Deionized water was distilled before use. Dioxane was purified as described by Fieser.[14] The solvent was prepared by mixing equal volumes of water and dioxane. Acid and base titers were stable under the reaction conditions to within ±1%. Spectrophotometric analysis of samples of solvent after subjection to the various reaction conditions showed no interfering absorbances.

The density of the solvent at the reaction temperatures was determined by measuring the volume of a known weight of solvent in a pycnometer which had a graduated neck and which had been calibrated with distilled water. The density data, Table VII, were used to correct concentrations for expansion of the solvent at reaction temperatures above 25.0°.

TABLE VII

SUMMARY OF THE DENSITY OF 50% AQUEOUS DIOXANE AT THE REACTION TEMPERATURES

Temp, °C	Density, g/ml
25.0	1.034
50.0	1.014
75.0	0.993
100.0	0.969
125.0	0.942

Measurement of Apparent pH.—All pH measurements were made at 25°. A solution of 0.001 *M* hydrochloric acid in 50% aqueous dioxane was defined as pH 3.0 and used to calibrate a glass electrode and calomel reference electrode for measurements of apparent pH of 1.45–10.7. The electrodes were equilibrated in 50% aqueous dioxane at least 24 hr before a measurement and were kept in the same solvent between measurements.

Owing to erratic electrode behavior, apparent pH values above 10.7 were determined by an indicator overlap method using thymol blue, clayton yellow, alizarin yellow R, and indigo carmine indicators.

Since no indicator was readily available with a pK_a large enough to allow measurement of the apparent pH of solutions with greater than 0.05 *M* sodium hydroxide, the pH was estimated from a plot of apparent pH for solutions of 0.00175 to 0.05 *M* sodium hydroxide *vs.* log (NaOH). Such a plot was linear with the intercept being equal to the pK_w, the negative log of the autoprotolysis constant, for 50% aqueous dioxane. The value obtained was 15.7 which agrees well with the value of 16.05 obtained by Baughman and Grunwald[15] using the potentiometric data of Harned and Fallon.[16]

---

[10] J. H. Elliot and M. Kilpatrick, *J. Phys. Chem.*, **45**, 485 (1941).

[11] M. Renson and J. Bidaine, *Bull. Soc. Chim. Belges*, **70**, 519 (1961).

[12] H. C. Brown, S. Johnson, and H. Podall, *J. Amer. Chem. Soc.*, **76**, 5556 (1954).

[13] M. J. Timmermans, *J. Chim. Phys.*, **56**, 984 (1959).

[14] L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Company, Boston, Mass., 1955, p 285.

[15] G. Baughman and E. Grunwald, *J. Amer. Chem. Soc.*, **80**, 3844 (1958).

[16] H. S. Harned and L. D. Fallon, *ibid.*, **61**, 2374 (1939).

Kinetic Procedure.—Solutions of *p*-toluenesulfonic acid were used at apparent pH of 1.45 and 1.95. For an apparent pH of 4.5 to 7.0, 2,6-lutidine–*p*-toluenesulfonic acid buffers were used and at apparent pH of 9.4 to 10.8, diisopropylethylamine–*p*-toluenesulfonic acid buffers were employed. The buffered solutions were prepared by diluting aliquots of stock solutions in 50% aqueous dioxane of the appropriate amine and of *p*-toluenesulfonic acid with solvent. Solutions of the desired buffer concentration and apparent pH were obtained by varying the aliquot volumes. Sodium hydroxide solutions were used at an apparent pH of 12.0 and above. Before use, the solutions were cooled in in an ice bath and deoxygenated by bubbling nitrogen through them for 30 min.

Sealed ampoules were employed for reactions run at 100–125°. For reactions at 25.0 and 50.0° glass bottles, which were fitted with silicone rubber seals and screw caps in which a hole had been drilled to allow removal of aliquots with a syringe during the reaction, were used.

Rate constants for the disappearance of ethyl thiobenzoate in 50% aqueous dioxane were calculated from data obtained by measuring the absorbance of the reaction sample at 414 mμ on a Beckman DU spectrophotometer equipped with a photomultiplier. The disappearance of ethyl thionbenzoate was also followed spectrophotometrically at 290 mμ after extraction of reaction samples by the procedure described below. The rate of hydrolysis of ethyl benzoate in 50% aqueous dioxane was determined by extracting reaction samples as described below and analyzing the extracts spectrophotometrically at 230 mμ.

Extraction Procedure.—An 2.016-ml aliquot of the reaction solution was added to a separatory funnel containing 10 ml of cyclohexane and 10 ml of 7% aqueous sodium bicarbonate. When the reaction was carried out in the presence of *p*-toluenesulfonic acid or sodium hydroxide, the aqueous layer was extracted with two additional 5-ml portions of cyclohexane. When an amine buffer was present, the aqueous bicarbonate layer was extracted with one additional 5-ml portion of cyclohexane, the combined extracts were then washed with 10 ml of 5% aqueous hydrochloric acid and the aqueous acid layer extracted with an additional 5-ml portion of cyclohexane. In each case, the combined extracts, *ca.* 20 ml, were diluted to 25 ml for spectrophotometric analysis. Extraction of aliquots of solutions of known ethyl thionbenzoate and ethyl benzoate concentration showed that the recovered amounts of each ester were within ±3% of the original concentration.

Determination of Ethyl Benzoate and Ethyl Thionbenzoate Concentrations During the Reaction.—In order to calculate values of k_2 from eq 4, it is necessary to determine the concentrations of both ethyl benzoate and ethyl thionbenzoate. For runs in the presence of sodium hydroxide, these esters were extracted from the reaction mixture and the absorbance was measured at both 230 and 290 mμ using a Beckman DU spectrophotometer which allows the desired concentrations to be calculated.

For runs at an apparent pH of 1.45 to 10.8, the concentrations of ethyl benzoate and ethyl thionbenzoate were calculated from quantitative gas chromatographic data. Aliquots of the reaction mixture were extracted as described for spectrophotometric analysis except that a known amount of a solution of ethyl phenylacetate in cyclohexane was added to each separatory funnel. The cyclohexane extracts were concentrated at 90–95° to *ca.* 0.5 ml by distilling the solvent through a 6-in. Vigreaux column. Injections of 0.15–0.25 ml samples were made into a 3.5-ft 20% KF-1150 on Chromosorb W column at 120° using an Aerograph A-90 gas chromatograph. The order of appearance of the compounds was ethyl benzoate, ethyl phenylacetate, and ethyl thionbenzoate. Peak areas were measured with a disk chart integrator. The area of the ethyl thionbenzoate peak was corrected for the minor peak in the internal standard by subtracting 0.6% of the area of the ethyl phenylacetate peak.

The calibrations were done by extracting and chromatographing aliquots of solutions of ethyl benzoate and ethyl thionbenzoate of known concentration in 50% aqueous dioxane. Analysis of samples of a solution of known concentrations of ethyl benzoate, ethyl phenylacetate, and ethyl thionbenzoate in cyclohexane before and after treatment with the above extraction procedure indicated that there was no change in relative peak areas within ±2%.

Registry No.—II, 936-61-8; III, 93-89-0; IV, 98-91-9.

Reductive Cyclization of α,ω-Dihalides with Chromium(II) Complexes

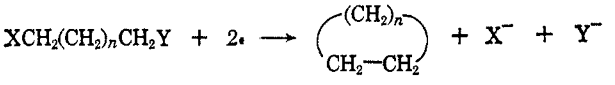
JAY K. KOCHI AND DAVID M. SINGLETON

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Received September 26, 1967

Various 3-substituted alkyl halides are readily reduced by ethylenediaminechromium(II) reagent in DMF solutions at room temperatures. γ-Dihalides and γ-halo tosylates are reductively cyclized in excellent yields to cyclopropanes. Protolytic reduction of the carbon–halogen bond is the most relevant competing reaction. The latter becomes significant when groups in the γ position of alkyl halides are hydroxy, acetoxy, phenoxy, amino, cyano, phthalimido, or triethylammonium. The role of chromous reagent in reductive cyclization is compared with the mechanism of protolytic reduction and the mechanism of reductive elimination of vicinally substituted alkyl halides. Similar free-radical and alkylchromium intermediates are involved in all of these reductive processes. Factors which determine the relative rates of cyclization and protonation of the metastable γ-substituted alkylchromium species are discussed. The effects of γ or β substituents in reductive cyclization or reductive elimination are compared and contrasted; leaving-group ability is considered to be an important attribute for γ substituents in cyclopropane formation. Evidence is presented for neighboring-group participation by a γ-iodine atom in the homolytic removal of the initial halogen by ligand transfer to Cr^{II}en. Stereochemical studies with *meso-* and *dl*-2,4-dibromopentanes show that there is no specificity in cyclopropane formation. Reductive cyclization of α,δ-dihalides and higher homologs with Cr^{II}en was not promising.

Reductive cyclization of α,ω-dihaloalkanes and derivatives is a useful method of preparing cycloalkanes. The stoichiometry of the process (half-reaction) is given by eq 1. Zinc,[1] magnesium,[2] and Grignard reagents[3] have been used as reducing agents. Recently, other novel methods for α,γ cyclization using allyl chloride and diborane[4] as well as azetidine and difluoramine[5] have been reported.



$$XCH_2(CH_2)_nCH_2Y + 2\cdot \longrightarrow \overbrace{CH_2{-}CH_2}^{(CH_2)_n} + X^- + Y^- \quad (1)$$

---

[1] R. Shortridge, R. Craig, K. Greenlee, J. Derfer, and C. Boord, *J. Amer. Chem. Soc.*, **70**, 946 (1948); **67**, 1863 (1945); (b) H. Haas, E. McBee, G. Hinds, and E. Glusenkamp, *Ind. Eng. Chem.*, **28**, 1178 (1936); M. Murray, *ibid.*, **66**, 812 (1944); J. Battleson, *ibid.*, **68**, 2153 (1946); V. Slabey, *ibid.*, **68**, 1335 (1946); H. Shechter, *Org. Syn.*, **44**, 30 (1964); P. Leriverend and J. Conia, *Bull. Soc. Chim. France*, 116 (1966).

[2] J. Grayson, K. Greenlee, J. Derfer, and C. Boord, *J. Org. Chem.*, **20**, 275 (1955); *J. Amer. Chem. Soc.*, **75**, 3344 (1953).

[3] N. Rabjohn and M. Cohen, *ibid.*, **74**, 6290 (1952); L. Slaugh, *ibid.*, **83**, 2734 (1961); M. Kharasch, M. Weiner, W. Nubenberg, A. Bhattacharya, T. Wang, and N. Yang, *ibid.*, **83**, 3232 (1961); M. Kharasch, J. Sallo, and W. Nudenberg, *J. Org. Chem.*, **18**, 575 (1953); **21**, 129 (1956); C. DePuy, G. Dappen, K. Eilers, and R. Klein, *ibid.*, **29**, 2813 (1964); W. Smith, *ibid.*, **23**, 509 (1958).

[4] N. Hawthorne, *J. Amer. Chem. Soc.*, **82**, 1886 (1960).

[5] C. Bumgardner, K. Martin, and J. Freeman, *ibid.*, **85**, 97 (1963).