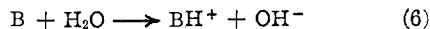nature of the system the rate constant k_5 cancels in the derivation of the expression for k_h/k_{ex}.

The rate constants for the reaction

$$B + H_2O \longrightarrow BH^+ + OH^- \qquad (6)$$

have been determined experimentally for a large number of oxy-anions and nitrogen bases. The rate constants of these reactions are to a first approximation directly proportional to the basicities of B, varying from 4×10^9 l./mole sec. for the reaction $OH^- + H_2O$ to 4×10^{-7} l./mole sec. for $H_2O + H_2O$.[19] If the pK_a of the tetrahedral intermediate is of the same order of magnitude as that for formaldehyde hydrate (5.1×10^{-14}),[20] one would expect that the value of the rate constant k_4 might be of the order of 10^8 l./mole sec. or 10^9 sec.$^{-1}$[21]. Since it has been shown previously that one need not consider the proton transfer in step k_5 because of the symmetry of the system, a consideration of k_4 alone leads to a proper kinetic assessment of the proton transfer possibilities in the tetrahedral intermediate. This consideration indicates that proton transfer, $k_4 \cong 10^9$ sec.$^{-1}$, is of the same order of magnitude as decomposition to products, $k_3 \cong 10^9$ sec.$^{-1}$ (a lower limit). These estimates account for the values of k_3 and k_4 calcu-

lated from the experimental data above, which are also of the same order of magnitude.

These crude considerations point to the possibility that proton transfer, k_4, may be kinetically significant with respect to decomposition to products, k_3. Therefore one cannot assume in the mechanism for concurrent hydrolysis and isotopic oxygen exchange that the proton transfers in the tetrahedral intermediate are kinetically insignificant (as was done before the days in which measurements of proton transfers were put on a sound experimental basis), but rather should assume that the proton transfer step may play an important part of the over-all mechanism. Certainly in the present instance, the striking substituent effects cannot be explained in terms of the earlier mechanism in which proton transfers were neglected, but can be explained readily if their presence is taken into account. A possible result of the importance of proton transfer in reactions of the tetrahedral intermediate is that deuterium isotope effects associated with these proton transfers will be measurable. Preliminary evidence to this effect has been obtained in these laboratories and is being pursued at the present time.

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The Concurrent Alkaline Hydrolysis and Isotopic Oxygen Exchange of Several Alkyl Benzoates and Lactones[1,2]

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The kinetics of the concurrent alkaline hydrolysis and isotopic oxygen exchange of methyl benzoate, p-chlorobenzyl benzoate, p-methoxybenzyl benzoate, phthalide and γ-butyrolactone have been determined. Only in the hydrolysis of methyl benzoate has concurrent oxygen exchange been found. In the other hydrolyses, the exchange reaction is not present within experimental error. A lower limit to the ratio k_h/k_{ex} in the latter reactions has been calculated. The surprising lack of oxygen exchange in the hydrolysis of the benzyl benzoates, as contrasted to that of the kinetically similar methyl benzoate, is attributed to the preferential partitioning of the tetrahedral intermediate to products to relieve steric strain in the intermediate caused by the bulky benzyloxy group.

Introduction

Concurrent carbonyl oxygen exchange and hydrolysis have been demonstrated in the hydrolyses of a number of benzoate esters including ethyl, isopropyl and t-butyl benzoates.[4] This concurrent hydrolysis and exchange has been interpreted in terms of the partitioning of an unstable tetrahedral addition intermediate of the form $RC(OH)_2$-

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(2) Paper XI in the series, Intermediates in the Reactions of Carboxylic Acid Derivatives. Previous paper, M. L. Bender and R. J. Thomas, J. Am. Chem. Soc., 83, 4189 (1961).

(3) (a) Alfred P. Sloan Foundation Research Fellow; (b) Department of Chemistry, Northwestern University, Evanston, Ill.

(4) M. L. Bender, J. Am. Chem. Soc., 73, 1626 (1951).

OR. The magnitude of the carbonyl oxygen exchange which accompanies hydrolytic reactions of carboxylic acid derivatives permits a description of the partitioning of the addition intermediate into reactants and products. In the previous paper,[2] for example, the effect of p-substituents on the partitioning of the tetrahedral intermediate in the alkaline hydrolysis of a series of p-substituted methyl benzoates was investigated. The results of that investigation led to the postulation that the proton transfers in the tetrahedral intermediate, which must take place to make the two oxygen atoms equivalent to one another (and thus which must take place for exchange to occur) are kinetically significant with respect to the decomposition

of the intermediate to products. The present paper deals with a number of alkaline hydrolyses of benzoate esters and lactones.

In the alkaline hydrolyses of ethyl, isopropyl and *t*-butyl benzoates, the ratio k_h/k_{ex} varies in a somewhat erratic manner, with all values being between 1 and 10.[4] On the other hand, in the alkaline hydrolysis of phenyl benzoate, it has been found that no isotopic oxygen exchange accompanies the hydrolytic reaction.[5] In an attempt to gain more information and to rationalize the behavior of the tetrahedral addition intermediates in the alkaline hydrolysis of esters containing different alkyl groups, we have investigated the concurrent hydrolysis and oxygen exchange of methyl benzoate-*carbonyl*-O^{18}, a series of *p*-substituted benzyl benzoates-*carbonyl*-^{18}O, phthalide-*carbonyl*-^{18}O and γ-butyrolactone-*carbonyl*-^{18}O.

Experimental

Materials.—Water, dioxane and the standard solutions were prepared as described in the previous paper.[2]

Unlabeled Compounds.—Benzyl alcohol, *p*-nitrobenzyl alcohol and *p*-methoxybenzyl alcohol were Eastman Kodak Co. products. *p*-Chlorobenzyl alcohol was prepared according to the directions of Hawthorne and Cram[6] in 70% yield, m.p. 73.5–74°. γ-Butyrolactone (Eastman Kodak Co.) was fractionally distilled *in vacuo*, b.p. 82–83° (13 mm.), n^{25}D 1.4345; lit. b.p. 89° (12 mm.),[7] n^{25}D 1.4348.[8] Phthalide (Matheson Co.) was used directly, m.p. 72–74°.

Labeled Compounds.—Methyl benzoate and the substituted benzyl benzoate esters labeled with oxygen-18 in the carbonyl group were prepared in the following way. Benzoic acid-^{18}O was prepared by treatment of benzoyl chloride with $H_2^{18}O$.[9] Benzoic acid-^{18}O was converted to benzoyl chloride-^{18}O by treatment with thionyl chloride and the labeled benzoyl chloride was treated with the appropriate alcohol in pyridine as solvent. The esters had essentially the same physical constants as the unlabeled materials reported in the literature.

γ-Butyrolactone-*carbonyl*-^{18}O was prepared according to the procedure of Long and Friedman.[10] The unlabeled γ-butyrolactone (2 ml., 0.026 mole) was equilibrated at 25° with 5 ml. of labeled water (1.6 atom % ^{18}O, Stuart Oxygen Co.) and 0.25 ml. of concentrated sulfuric acid for 5 days. The γ-butyrolactone-*carbonyl*-^{18}O was continuously extracted with benzene for several hours and distilled *in vacuo*, b.p. 85° (14 mm.), n^{25}D 1.4297.

Phthalide-*carbonyl*-^{18}O was also prepared by an equilibration procedure. Phthalide (5.31 g., 0.40 mole), dissolved in 25 ml. of ethanol (for solubilization), 35 ml. of labeled water (1.6 atom % ^{18}O, Stuart Oxygen Company) and 1.5 ml. of concentrated sulfuric acid, was refluxed for 40 hours. Ethanol and water were removed by distillation and the phthalide-*carbonyl*-^{18}O was recrystallized from ethanol–water, m.p. 74.5–75.5°, lit.[11] m.p. 75°.

Kinetics of Hydrolysis.—The kinetics of the alkaline hydrolyses of methyl benzoate, *p*-methoxybenzyl benzoate, benzyl benzoate, *p*-chlorobenzyl benzoate, *p*-nitrobenzyl benzoate and phthalide were determined by acid–base titration. At appropriate times, aliquots were withdrawn from the reaction mixture, discharged into excess standard hydrochloric acid and back-titrated with standard dilute sodium hydroxide to a phenolphthalein end-point. The rate of the alkaline hydrolysis of γ-butyrolactone was followed by measuring the change in conductance of the reaction mixture during the reaction. A General Radio Co. type 650-A impedance bridge and 650-PI oscillator amplifier were used.

Oxygen Exchange.—Samples of the esters enriched in *carbonyl*-^{18}O were partially hydrolyzed under conditions approximately the same as those used in the hydrolytic experiments. After the appropriate time interval, the unreacted labeled ester was recovered as follows. The reaction was quenched with an appropriate amount of dilute hydrochloric acid and the unreacted ester was recovered from the aqueous phase by extraction. γ-Butyrolactone was recovered by continuous extraction with benzene. Phthalide was recovered by continuous extraction with ether. Methyl benzoate and the benzyl benzoates were recovered by extracting with five portions of methylene chloride. The solid esters were purified by recrystallization from methanol–water or ethanol–water solution until the melting point agreed closely with the literature value. The liquid esters, methyl benzoate and γ-butyrolactone, were purified by micro vacuum distillation. The oxygen-18 content of the ester samples was determined by converting them to carbon dioxide and analyzing the carbon dioxide samples for their oxygen-18 content with a Consolidated–Nier model 21–201 isotope-ratio mass spectrometer. The ester samples were converted to carbon dioxide by either the method of Rittenberg and Ponticorvo[12] or the method of Doering and Dorfman.[13]

Results

The second-order rate constants for the alkaline hydrolysis of the various esters are listed in Table I. A Hammett plot of the kinetic data for the *p*-substituted benzyl benzoates shows a reasonably good linear relationship with a slope (ρ) of +0.91. The effects of substituents on the hydrolysis of the substituted benzyl esters in 66²/₃ dioxane–water is less than that of substituted phenyl esters in

TABLE I

ALKALINE HYDROLYSIS OF SOME ALKYL BENZOATES AND LACTONES[a]

Ester	$k_2 \times 10^3$ l./mole sec., 66²/₃%, dioxane–water[f]	33¹/₃% dioxane–water	Water
p-Nitrobenzyl benzoate	30.5 = 1.2[e]		
p-Chlorobenzyl benzoate	9.44 ± 0.11	18.3 ± 0.7[g]	
Benzyl benzoate	5.29 ± .07		
p-Methoxybenzyl benzoate	3.83 ± .06		
Methyl benzoate		23.2 ± 0.4	
Phthalide		144 ± 11	255 ± 12[d]
γ-Butyrolactone[b]			185 ± 15[c]

[a] 24.8 ± 0.1° unless otherwise noted. [b] 0.1°. [c] Lit.[14] value; 0.197 l./mole sec. [d] Lit.[14] value, 0.224 l./mole sec. [e] Average deviation for repeated runs. [f] Solvents: volume/volume. [g] 50% dioxane–water, v./v.

water where a ρ of 1.1 is found,[15] but the difference between the benzyl and phenyl esters is surprisingly small. This similarity in the susceptibility of the two families of esters to substituent effects may be due to the fact that in both instances the substituent effect is manifested in the step in which hydroxide ion is added to the carbonyl carbon atom forming the tetrahedral intermediate and not in the subsequent step in which the alkoxide ion is formed. Since the ρ's of both families of reactions are similar, one may say that in both processes the leaving of the alkoxide ion is not a part of the kinetically im-

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(8) C. McKinley and J. P. Copes, *J. Am. Chem. Soc.*, **72**, 5331 (1950).

(9) Stuart Oxygen Co., San Francisco, Calif.

(10) F. A. Long and F. Friedman, *J. Am. Chem. Soc.*, **72**, 3692 (1950).

(11) I. M. Heilbron, "Dictionary of Organic Compounds," Oxford Univ. Press, New York, N. Y., 1934.

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(13) W. E. Doering and E. Dorfman, *ibid.*, **75**, 5595 (1953); see M. L. Bender and K. C. Kemp, *ibid.*, **79**, 116 (1957).

(14) D. S. Hegen and J. H. Wolfenden, *J. Chem. Soc.*, 508 (1939).

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portant step of the reaction, for if it were the susceptibility of the phenyl esters to substituents should be much greater than that of the benzyl esters.

The oxygen exchange data for the various esters and lactones are given in Table II.

TABLE II
OXYGEN EXCHANGE ACCOMPANYING THE BASIC HYDROLYSIS OF BENZOATE ESTERS AND LACTONES

Reaction, %	Excess atom % $^{18}O^g$	k_h/k_{ex}	Reaction, %	Excess atom % $^{18}O^g$	k_h/k_{ex}
p-Chlorobenzyl benzoate[b]			*p*-Methoxybenzyl benzoate[b]		
0	0.571		0	0.401	
45.1	.568		22.3	.391	
53.9	.585		56	.391	
60.8	.586		78.4	.386	>192
66.2	.593		Phthalide[d]		
71.1	.593		0	1.302	
71.1	.577		25	1.205	
74	.593		50	1.230	
77	.577	>150[a]	75	1.322	>50
p-Chlorobenzyl benzoate[b]			γ-Butyrolactone[e,f]		
0	0.563		0	0.983	
16.5	.546		25	.876	
60.3	.569		50	.906	
76	.550		75	1.031	>80
83.7	.565	>180	Methyl benzoate[d]		
p-Chlorobenzyl benzoate[c]			0	0.637	
			15	.612	
0	4.61		30	.600	
50	4.30		45	.585	
75	4.55	>60	60	.538	5.2 ± 0.8

[a] These approximations have been made on the basis that the oxygen exchange at the highest fraction of hydrolysis is assumed to have occurred to the extent of the average deviation of all the experimentally determined oxygen-18 analyses, using eq. 1. [b] Solvent, $66^2/_3\%$ dioxane–water v./v. [c] Solvent, 50% dioxane–water v./v. [d] Solvent, $33^1/_3\%$ dioxane–water v./v. [e] Solvent, water. [f] The average deviation in this run is particularly high because of difficulties in purification of this liquid lactone. [g] In the carbonyl group.

Table II indicates the surprising result that both *p*-chlorobenzyl benzoate and *p*-methoxybenzyl benzoate, as well as phthalide and γ-butyrolactone, hydrolyze with essentially no concurrent oxygen exchange. Since an error exists in the oxygen-18 analysis, it is not possible to make an absolute statement about the presence or absence of oxygen exchange in these reactions, but only to set a lower limit on k_h/k_{ex}. These lower limits are based on the assumption that oxygen exchange may occur at the highest fraction of hydrolysis to the extent of the average deviation of all the experimentally determined oxygen-18 analyses. The limiting value of k_h/k_{ex} may be computed from the expression

$$k_h/k_{ex} = \log (1 - f)/\log (1 - u) \qquad (1)$$

where f is the fraction of hydrolysis and u is the average deviation in the oxygen-18 determinations. It is seen that in favorable cases where the average deviation is small, one can set a lower limit on k_h/k_{ex} which is in the range of 150 to 200. But when the average deviation is large, the lower limit

is as low as 30 to 50. These difficulties of course arise from the fact that the exchange reaction is not the sole reaction occurring but is accompanied by the hydrolysis reaction which consumes the material under observation and thus prevents long term observation of the exchange reaction. In this regard it should be noted that it is desirable to isolate the reactant at the highest possible percentage reaction in order to get the highest value of the lower limit of k_h/k_{ex}. For example, in the acidic hydrolysis of benzamide, it was possible to isolate some starting material after 84.5% reaction and thus to set a lower limit on k_h/k_{ex} of 374.[16]

Discussion

The most interesting result of these investigations is the lack of isotopic oxygen exchange that has been found in reactions closely similar to reactions in which oxygen exchange had been found previously. The closest comparison is that between the simple alkyl benzoates such as methyl, ethyl, isopropyl and *t*-butyl benzoates which show extensive carbonyl oxygen exchange and the benzyl benzoates which show essentially no oxygen exchange. The values of the oxygen exchange accompanying these hydrolytic reactions are summarized in Table III. It is seen that oxygen exchange accompanies the alkaline hydrolysis of all four simple alkyl benzoates, although it is difficult to rationalize the small variations noted among the values of k_h/k_{ex}. One would predict, on the basis

TABLE III
OXYGEN EXCHANGE ACCOMPANYING THE HYDROLYSIS OF SOME BENZOATE ESTERS AT 25.0°

Benzoate	k_h/k_{ex}	Solvent	Ref.
Methyl	5.8	a	f
Ethyl	10.6	a	4
Isopropyl	5.4	b,c	4
t-Butyl	11.4	b	4
p-Methoxybenzyl	>192	d	f
p-Chlorobenzyl	>150[g]	d,e	f
Phenyl	>105	e	5

[a] $33^1/_3\%$ dioxane–water. [b] $33^1/_3\%$ dioxane–water, extrapolated from 62.5° using the temperature coefficient for ethyl benzoate oxygen exchange. [c] Extrapolated from water solvent, using the solvent effect found for ethyl benzoate. [d] $66^2/_3\%$ dioxane–water. [e] 50% dioxane–water. [f] This research. [g] Median of the three experimental values; see Table II.

that the partitioning is affected solely by the stability of the departing anion, that methyl benzoate would exhibit the highest k_h/k_{ex}. On the other hand, one would predict, on the basis that the partitioning is affected solely by the relief of steric strain in the tetrahedral intermediate, that *t*-butyl benzoate would exhibit the highest k_h/k_{ex}. Of course the data are not explained even by these two reasonable, but opposing effects. No attempt will be made at this time to introduce a third parameter to explain the small variations exhibited by the simple alkyl benzoates, especially since two of the values involve temperature extrapolations.

Table III also indicates the wide discrepancy between the oxygen exchange accompanying the hydrolysis of simple alkyl benzoates and that

(16) M. L. Bender and R. D. Ginger, *J. Am. Chem. Soc.*, **77**, 348 (1955).

accompanying the hydrolysis of two benzyl benzoates. The second-order alkaline hydrolysis rate constants for the simple alkyl benzoates and the benzyl benzoates are of the same order of magnitude, as can be seen from a comparison of the hydrolysis of methyl benzoate in $33^1/_3\%$ dioxane-water and of p-chlorobenzyl benzoate in 50% dioxane–water (Table I). The rate constants for the two reactions mentioned above differ from one another by less than 25%. Yet the ratios k_h/k_{ex} for these two reactions differ from one another by a minimum of 30-fold. This difference in k_h/k_{ex} could of course be much larger, but experimental uncertainty on the value for p-chlorobenzyl benzoate sharply limits the precision with which one can say that k_h/k_{ex} approaches infinity.

One reason for a difference in k_h/k_{ex} suggested above is a difference in the basicity of the departing alkoxide ion. This reason cannot account for the difference between methyl benzoate and p-chlorobenzyl benzoate for it has been shown that methoxide ion and benzyloxide ion have approximately the same basicity.[17] The difference in the basicity of the leaving group has been suggested as the reason that phenyl benzoate shows no oxygen exchange ($k_h/k_{ex} > 105$) while methyl benzoate does.[5] This argument seems plausible since phenoxide ion has a K_a about five powers of ten lower than that of methoxide ion. But this same argument would predict that no oxygen exchange would be observed in the hydrolysis of benzoic anhydride where the pK_a of the benzoate leaving group is about 5. However, it has been found that the (neutral) hydrolysis of benzoic anhydride does indeed exhibit concurrent oxygen exchange.[18] These comparisons, all involving reactions in which oxy anions are the leaving groups, leave unsettled the question of the importance of the stability of the departing anion.

On the other hand, the lack of isotopic oxygen exchange in the benzyl and phenyl benzoates may be attributed to the steric requirements of these bulky groups, in view of the observation of steric hindrance in stable tetrahedral addition compounds.[19] However, it would be expected that the bulk of the benzoyloxy group would approximate the bulk of the phenoxy or benzyloxy groups and thus one would expect that the former would also exhibit no oxygen exchange. Furthermore it should be noted that the t-butyloxy group, which is probably more bulky than either the benzyloxy or phenoxy groups, permits oxygen exchange. It thus appears that no simple explanation is at hand to explain the behavior of these tetrahedral addition intermediates although the steric effect seems to be the best idea at the moment. It should be pointed out, however, that the differences being observed in k_h/k_{ex} may not be any greater than one or two orders of magnitude and therefore we may be still dealing with rather subtle effects.

It has been mentioned before that when the ratio k_h/k_{ex} is much greater than one, the partitioning of the intermediate does not affect the over-all

rate constant to an appreciable extent.[2] Thus one can say that in all the cases in Table III where k_h/k_{ex} is much greater than one, the hydrolytic rate constant approximately equals the rate constant for addition of hydroxide ion to the carbonyl group of the ester.

The results of the investigation of the two lactone hydrolyses shown in Table III indicate that there is no appreciable exchange accompanying the hydrolysis of lactones. Although it has been pointed out that the hydrolysis of lactones in the aliphatic series is faster than the hydrolysis of the corresponding open chain esters[20-22] the hydrolysis of phthalide is only fivefold faster than that of methyl benzoate, its open chain analog. This lack of reactivity of phthalide, relative to its open chain analog, can be explained on the basis that the carbonyl group in phthalide is restricted to coplanarity with the benzene ring whereas the carbonyl group in methyl benzoate is not. Therefore it would be expected that the reasonance stabilization in the former compound would be greater than that in the latter compound and that the former would therefore be less reactive than otherwise might have been anticipated. As mentioned in the preceding paragraph, when the ratio k_h/k_{ex} is much greater than one, the partitioning of the intermediate does not affect the over-all hydrolytic rate constant to an appreciable extent. Therefore in the hydrolysis of methyl benzoate and the hydrolysis of phthalide, the hydrolytic rate constant is not affected by the difference in partitioning and probably in all comparisons between lactones and open chain esters the difference in reactivity must be sought elsewhere than in the partitioning of the tetrahedral intermediate.

In the present series of papers it has been possible in certain instances to specify the transformations of the tetrahedral intermediates in hydrolytic reactions of carboxylic acid derivatives. The proton transfers in the tetrahedral intermediate in the hydrolysis of acetanilides have been described in a qualitative way. The proton transfers in the tetrahedral intermediate in the hydrolysis of methyl benzoates have been described in a semiquantitative manner. Investigations of the alkaline hydrolysis of a series of alkyl benzoates indicates that oxygen exchange does not always accompany the hydrolysis reaction. Although suggestions have been made to explain the latter results on the basis of electronic and steric effects on the partitioning of the tetrahedral intermediate, no completely self-consistent set of explanations is presently available to explain all the data. It is apparent that some new approach is necessary to explain the radically different behavior of the two similar tetrahedral intermediates derived from methyl benzoate and benzyl benzoate.

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