

ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL., AND NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

The Concurrent Alkaline Hydrolysis and Isotopic Oxygen Exchange of a Series of *p*-Substituted Acetanilides^{1,2}BY MYRON L. BENDER³ AND ROBERT J. THOMAS

RECEIVED MAY 13, 1961

The kinetics of the concurrent alkaline hydrolysis and carbonyl oxygen exchange of a series of *p*-substituted acetanilides have been investigated. The kinetics of hydrolysis are complicated, involving terms both first and second order in hydroxide ion. Significant carbonyl oxygen exchange occurred under conditions in which 90% of the reaction proceeded *via* a process first order in hydroxide ion. The effect of substituents on the over-all hydrolytic rate constant is small. From the hydrolysis and oxygen exchange data, the effects of substituents on k_1 , the formation of the tetrahedral intermediate, and on k_3/k_2 , the partitioning of the intermediate to products and reactants, were determined. Electron-withdrawing substituents increase k_1 ($\rho +1.0$) and decrease k_3/k_2 ($\rho -1.0$), leading to an over-all cancellation of substituent effects (ρ of $k_b = +0.1$). On the basis of the substituent effect on k_3/k_2 , it is postulated that the breakdown of the tetrahedral addition intermediate to give products must involve the formation of the dipolar ion, $\text{CH}_3\text{C}(\text{O}^-)_2\text{NH}_2^+\text{C}_6\text{H}_4\text{X}$. This phenomenon is thought to be a general property of amide hydrolyses and other hydrolyses where a negative leaving group would involve a species of very high basicity.

Introduction

Concurrent carbonyl oxygen exchange and hydrolysis have been demonstrated for the hydrolyses of a number of benzoate esters, acid chlorides and benzamide.^{4,5} This concurrent hydrolysis and exchange has been interpreted in terms of the partitioning of an unstable tetrahedral addition intermediate of the form $\text{RC}(\text{OH})_2\text{X}$ where X corresponds to an alkoxyl group in the case of an ester, a chloride group in the case of an acid chloride or an amido group in the case of an acid amide. The determination of the magnitude of the carbonyl oxygen exchange which accompanies hydrolytic reactions of various carboxylic acid derivatives permits a more precise specification of the mechanism of the reaction and, in particular, permits a description of the breakdown (partitioning) of the addition intermediate into reactants and products. Recently the effect of temperature and solvent on the isotopic oxygen exchange accompanying the hydrolysis of amides and esters was determined.^{2,6} This series of papers describes investigations of the effect of structural parameters on isotopic exchange accompanying various hydrolytic reactions, with a view toward determining rules for the partitioning of the postulated intermediates in these reactions.

The present paper describes an investigation in which the electronic nature of the leaving group has been systematically changed in order to determine the effect of electronic donation or withdrawal on the partitioning of the tetrahedral intermediate. Through the elucidation of these

electronic effects on the partitioning of the tetrahedral intermediate it has been possible to describe the fate of this intermediate in detailed terms, and in particular the proton transfers which are necessary for its decomposition to form products.

The compounds selected for this study were a series of *p*-substituted acetanilides. These compounds were chosen because it was known from previous investigations that the alkaline hydrolysis of an amide is accompanied by the largest amount of carbonyl oxygen exchange exhibited by any carboxylic acid derivative.^{4,5} In fact, in the hydrolysis of benzamide in 66²/₃% dioxane-water the rate constant for exchange is 17 times greater than that of hydrolysis.² It was deemed desirable to have as great an amount of oxygen exchange as possible in order to maximize the range of observable exchange.⁷ The effect of temperature⁶ and solvent² on the concurrent alkaline hydrolysis and carbonyl oxygen exchange of benzamide has been investigated in detail. However, no effects of structural parameters on these reactions have been determined, except that k_b/k_{ex} for the alkaline hydrolysis of *n*-butyramide is somewhat greater than that for benzamide under comparable conditions.⁸ In order to determine the effect of changes in the electronic character of the leaving group of an amide, without invoking extraneous steric effects, it was decided to investigate the carbonyl oxygen exchange accompanying the alkaline hydrolysis of a series of *p*-substituted acetanilides.

The kinetics of basic hydrolysis of a series of *N*-methyl-anilides was investigated by Beichler and Taft⁹ who found that the rate was dependent on both the polar and steric characteristics of the acyl group. These factors manifest themselves in the same way as in basic amide hydrolysis: bulky groups lower the rate by steric hindrance and electron-donating groups lower the rate by

(1) This research was supported by grants from the National Science Foundation and the U. S. Atomic Energy Commission.

(2) Paper IX in the series, Intermediates in the Reactions of Carboxylic Acid Derivatives. Previous paper, M. L. Bender and R. D. Ginger, *Suomen Kem.*, **B33**, 25 (1960).

(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); M. L. Bender, R. D. Ginger and K. C. Kemp, *ibid.*, **76**, 3350 (1954); M. L. Bender and R. D. Ginger, *ibid.*, **77**, 348 (1955).

(5) C. A. Buntton, T. A. Lewis and D. R. Llewellyn, *Chemistry & Industry*, 1154 (1954).

(6) M. L. Bender, R. D. Ginger and J. P. Unik, *J. Am. Chem. Soc.*, **80**, 1044 (1958).

(7) The limit of normal observation of carbonyl oxygen exchange is reached when the ratio of k_b/k_{ex} is greater than 100, utilizing compounds labeled with ca. 1% ¹⁸O.

(8) R. D. Ginger, unpublished observations.

(9) S. S. Beichler and R. W. Taft, *J. Am. Chem. Soc.*, **79**, 4927 (1957).

decreasing the electrophilic character of the carbonyl carbon atom. There is, however, a significant difference between basic amide and anilide hydrolysis: in the former reaction the rate is first order in hydroxide ion while the rate expression for the latter has two terms, one being first order in hydroxide ion and the other being second order in hydroxide ion. This kinetic dependence has been observed in the present experiments also, where the hydrolysis as well as the carbonyl oxygen exchange has been investigated.

Experimental

Materials. Water.—Water for kinetic measurements was tap distilled water which was redistilled once from alkaline permanganate through a glass bead-packed column.

Dioxane.—1,4-Dioxane (Matheson, practical) was purified by the method of Fieser¹⁰ and stored in brown bottles under nitrogen; n_D^{20} 1.4223.

Standard Solutions.—Carbonate-free sodium hydroxide (J. T. Baker, reagent) was prepared, standardized against potassium acid phthalate (Eastman Kodak Co., primary standard) and stored in polyethylene bottles with Ascarite drying tubes. Hydrochloric acid (Baker and Adamson, reagent) was standardized against sodium hydroxide.

Unlabeled Compounds.—Acetanilide and *p*-anisidine were Eastman Kodak Co. products and were recrystallized twice from water. *p*-Chloroacetanilide, *p*-acetotoluidide and *m*-nitroacetanilide were prepared from the corresponding amine and acetic anhydride using the Schotten-Baumann procedure. The products were recrystallized twice from water.

Preparation of Oxygen-18 Labeled Compounds. Acetyl Chloride-¹⁸O.—Ten grams of H₂¹⁸O (Stuart Oxygen Co., 1.4 atom % ¹⁸O) was added dropwise to 39 g. of acetyl chloride (Baker and Adamson reagent) and allowed to stand for 1 week, protected from atmospheric moisture. The labeled acid was reconverted to the acid chloride by adding 23 g. of phosphorus trichloride (Eastman Kodak Co., practical). To remove the hydrogen chloride formed, the solution was warmed to 40° for 1 hour after which the temperature was raised and the distillate which had a boiling point of less than 53° was collected. This distillate was redistilled and the fraction boiling at 48–53° was collected. This fraction, acetyl chloride-¹⁸O, was used to prepare the labeled acetanilides.

Carbonyl-¹⁸O-labeled Acetanilides.—The pure aniline was dissolved in pyridine by warming. The requisite amount of acetyl chloride-¹⁸O was added drop by drop and the resulting slushy mixture was allowed to stand for several days. The mixture was decanted into 250 ml. of water and dissolved by heating; decolorizing charcoal was added, and the solution was filtered hot and allowed to crystallize. The acetanilides-*carbonyl*-¹⁸O were recrystallized from water and vacuum dried.

Kinetics of Hydrolysis.—The rates of hydrolysis of the acetanilides were measured spectrophotometrically at a convenient wave length using a Beckman DU spectrophotometer. The initial acetanilide concentration was of the order of 10⁻⁴ to 10⁻⁵ M, the initial (and final) hydroxide ion concentration was 0.25 to 0.96 M and the ionic strength was maintained at 0.96 with sodium chloride. Since the hydroxide ion was always present in very large excess, the reaction exhibited pseudo-first-order kinetics. To obtain the first-order rate constant, k_h , the absorbance data were plotted in one of two ways: (1) if A_∞ was determined (after ten half-lives), a plot of $\log(A_t - A_\infty)$ vs. time was made; or (2) if A_∞ was not determined, the data were plotted by the method of Guggenheim in which a plot of $\log(A_t - A_t + 2.5 \text{ half-lives})$ vs. time was made.¹¹

Oxygen Exchange.—Samples of the anilides enriched in *carbonyl*-¹⁸O were partially hydrolyzed under conditions identical with those used in the hydrolytic experiments. After the appropriate time interval, the unreacted acetanilide-*carbonyl*-¹⁸O was recovered as follows. If the time for a desired percentage of reaction was less than 2 hours, the

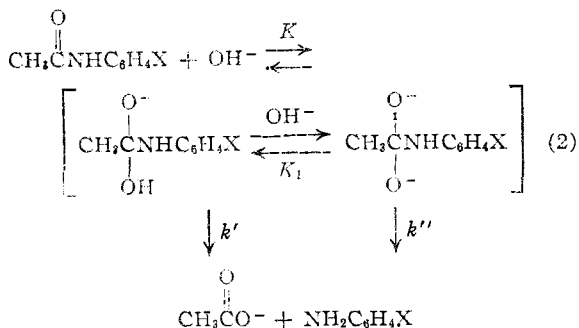
reaction was quenched by pouring the reaction mixture into hydrochloric acid. If the time was more than 2 hours, the reaction mixture was extracted without quenching, since the total time of extraction was less than 10 minutes. The unreacted acetanilide-*carbonyl*-¹⁸O was recovered from the aqueous phase by six 25-ml. methylene chloride extractions. Aniline, also extracted by methylene chloride, was removed by washing five times with 10 ml. of hydrochloric acid followed by three washings with water. The methylene chloride solution was dried with sodium sulfate; the methylene chloride was removed by heating and the residue, the acetanilide-*carbonyl*-¹⁸O, was recrystallized from water until its melting point agreed closely with the literature value. The oxygen-18 content of the acetanilide 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 acetanilide sample was converted to carbon dioxide by heating it at 500° for 2 hours in the presence of mercuric chloride (Fisher reagent).¹² Quinoline (Matheson, vacuum distilled from zinc dust; n_D^{25} 1.6250) was routinely used to absorb the by-product hydrogen chloride; ordinarily the pyrolysis products were introduced into quinoline twice to remove the hydrogen chloride. The reproducibility of the method, determined by pyrolyzing a series of identical samples of benzamide-¹⁸O, indicated a precision of $\pm 1\%$.¹³

Results and Discussion

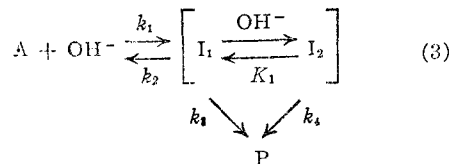
The kinetics of the alkaline hydrolysis of a series of *N*-methylacylanilides was found by Beichler and Taft to conform to a rate law

$$\text{rate} = [k_1(\text{OH}^-) + k_2(\text{OH}^-)^2](\text{N-methylacylanilide}) \quad (1)$$

That is, the rate is the sum of two terms, one first order in hydroxide ion and another second order in hydroxide ion. On the basis of this kinetic result, Beichler and Taft proposed the mechanism



The pre-equilibrium postulated in the first step of eq. 2 cannot be correct, for, as will be demonstrated later, complete oxygen exchange, predicted by the above formulation, does not accompany the hydrolytic reaction. Therefore we shall first modify this process by changing the initial step from an equilibrium to a rate process. This formulation can be represented as



Assuming the steady state approximation with respect to the intermediate, it may readily be

(12) D. Rittenberg and L. Ponticorvo, *J. App. Radiation and Isotopes*, **1**, 208 (1956).

(13) This is identical with the precision obtained by pyrolysis over carbon: K. C. Kemp, Doctoral Dissertation, Illinois Institute of Technology, 1957.

(10) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 3rd ed. rev., 1957, p. 284.

(11) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

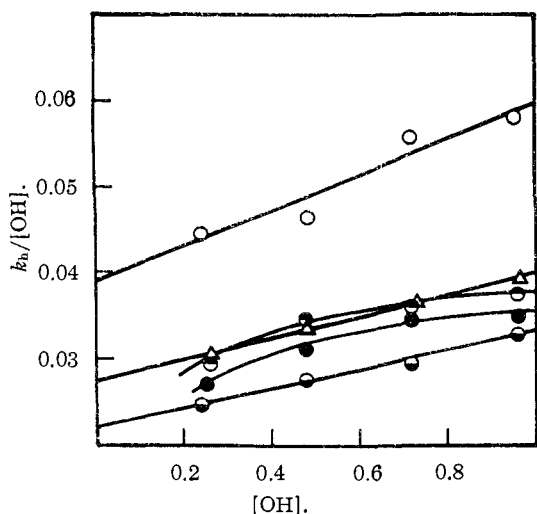


Fig. 1.—Kinetics of hydrolysis of substituted acetanilides in aqueous solution at 24.84° ($\mu = 0.962$): O, *m*-NO₂; Δ , *p*-Cl; \bullet , *p*-H; \bullet , *p*-CH₃O; \ominus , *p*-CH₃.

shown that

$$\frac{dP}{dt} = \left[\frac{k_1 k_3 (\text{OH}^-)}{k_2 + k_3 + k_4 K_1 (\text{OH}^-)} + \frac{k_1 k_4 K_1 (\text{OH}^-)^2}{k_2 + k_3 + k_4 K_1 (\text{OH}^-)} \right] \quad (\text{A}) \quad (4)$$

where the bracketed quantity is the pseudo-first order hydrolytic rate constant, k_h , experimentally determined in these reactions. If one can neglect $k_4 K_1 (\text{OH}^-)$ with respect to k_2 , k_3 or $(k_2 + k_3)$, a plot of $k_h/(\text{OH}^-)$ vs. (OH^-) will be linear, while if it cannot be neglected such a plot will exhibit curvature (concave downward). The kinetic data for the alkaline hydrolysis of five acetanilides (*m*-nitro, *p*-chloro, *p*-hydrogen, *p*-methyl and *p*-methoxy) studied at four hydroxide ion concentrations (0.24, 0.48, 0.72 and 0.96 *M*) are shown as a plot Fig. 1 of $k_h/(\text{OH}^-)$ vs. (OH^-) . It is seen that three of the curves are essentially linear while the other two exhibit a non-linear relationship which is concave downward. Since two of the behaviors predicted by the above relationship are found, it is reasonable to assume that eq. 3 is a fair representation of the hydrolysis.¹⁴ One further point should be noted in Fig. 1: the effect of substituents on both hydrolytic rate constants is very small. Furthermore the *p*-methoxy substituent is qualitatively out of line with respect to the other substituents (see Fig. 1). The Hammett relationship is illustrated for one set of conditions of k_h/OH in Fig. 3 ($\rho + 0.1$).

The Hydrolytic Process First Order in Hydroxide Ion.—In order to study the oxygen exchange accompanying the hydrolysis of these anilides it is of course desirable to be able to separate the two reactions, the one dependent on the first power of hydroxide ion and the one dependent on the second power. It is reasonably easy to isolate the reaction which is first order in hydroxide ion by working at relatively low hydroxide ion concentrations (because of the relative rates of the two processes). Therefore it is possible to concentrate on the simpler

(14) The ratio of the intercept to the slope of the lines in Fig. 1 is $k_3/k_4 K_1$ (see eq. 4). From the data in Fig. 1 it is seen that the values of $k_3/k_4 K_1$ are usually equal to or greater than unity.

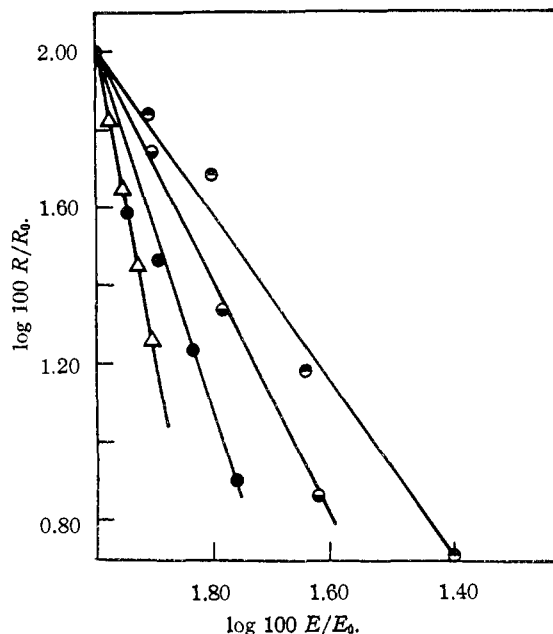
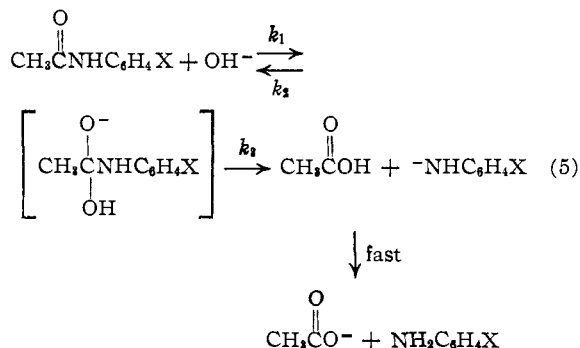


Fig. 2.—Oxygen exchange during the hydrolysis of substituted acetanilide in aqueous solution at 24.84° ($\mu = 0.962$, $[\text{OH}] = 0.239$): Δ , *p*-Cl; \bullet , *p*-H; \bullet , *p*-CH₃O; \ominus , *p*-CH₃.

process dependent only on the first power of the hydroxide ion concentration. To this end, the oxygen exchange during the hydrolysis of four substituted acetanilides in 0.239 *M* sodium hydroxide was investigated. Under these conditions the kinetics indicate that over 90% of the hydrolysis proceeds *via* the reaction first order in hydroxide ion concentration. The oxygen exchange data for these reactions are shown in Fig. 2, which indicates a linear relationship between the logarithm of the oxygen-18 content of the unreacted anilide and the logarithm of the extent of the hydrolysis reaction. The slopes of these lines can be shown to be equal to k_h/k_{ex} .⁴

In order to interpret these oxygen exchange data let us consider that the alkaline hydrolysis of the acetanilides occurs *via* a process paralleling those proposed earlier for ester and amide hydrolysis.



This formulation is the simplest possible mechanism that will qualitatively account for both hydrolysis and carbonyl oxygen exchange (assuming that the two oxygen atoms of the tetrahedral intermediate will equilibrate *via* rapid proton transfers). Under these conditions it has been shown that $k_h = k_1/(k_2/k_3) + 1$ and further that k_h/k_{ex}

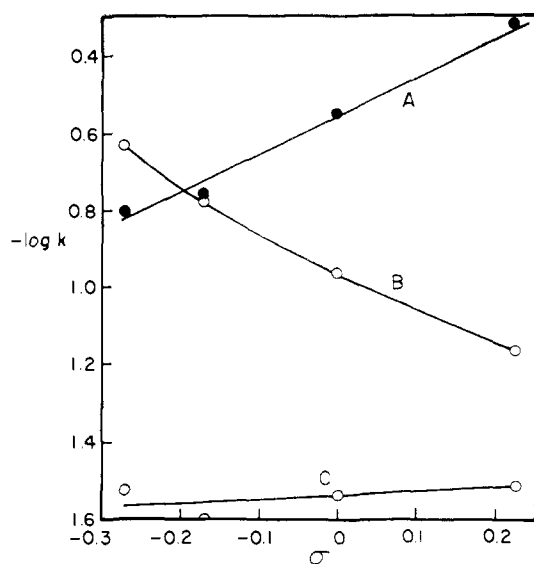


Fig. 3.—Substituent effects in concurrent hydrolysis and oxygen exchange of four substituted acetanilides ($[\text{OH}^-] = 0.239 M$; $\mu = 0.957$; temperature $24.7 \pm 0.1^\circ$): A, $-\log k_1$; B, $-\log k_3/k_2$; C, $-\log(k_h/[\text{OH}^-]) = \log(k_1/((k_2/k_3) + 1))$.

$= 2k_3/k_2$ and $k_1 = 2k_{\text{ex}} + k_h$. By using the experimental data shown in Fig. 2, it is then possible to calculate both k_1 , the rate constant for the formation of the tetrahedral intermediate, and k_2/k_3 , the rate constant ratio for the partitioning of the tetrahedral intermediate. From these data it is possible to determine the substituent effect on both the formation of the tetrahedral intermediate and its partitioning.

As mentioned above there is little effect of substituents on the over-all hydrolysis constant and this small effect is complicated by the curvature of some of the plots of $k_h/(\text{OH}^-)$ vs. (OH^-) and by the fact that *p*-methoxyacetanilide is qualitatively out of line. However a Hammett relationship involving $\log k_1$, related to the step involving the formation of the tetrahedral intermediate, for the various compounds and the respective Hammett substituent constants σ , is shown in Fig. 3. This approximately linear relationship has a slope of $+1.0$. This slope indicates that electron-withdrawing groups facilitate addition to the carbonyl group as expected.

A Hammett relationship between the log of the ratio of rate constants determining partitioning, k_3/k_2 , and sigma is most interesting. If the mechanism in eq. 5 were correct, one would expect electron-withdrawing substituents to favor hydrolysis (k_3) over exchange (k_2), since such substituents would stabilize the anionic leaving group. The results of the oxygen exchange study as seen in Fig. 3 show that electron-withdrawing substituents favor exchange over hydrolysis, just the opposite of the above prediction. Furthermore, the variation is substantial, k_3/k_2 varying from 0.068 for *p*-chloroacetanilide to 0.234 for *p*-methoxyacetanilide. The slope of the slightly curved plot of $\log k_3/k_2$ vs. σ in Fig. 3 is approximately -1.0 .

If the substituent effects on the various steps are additive, the effect of substituents on k_1 , the for-

mation of the tetrahedral intermediate ($+1.0$), and on k_3/k_2 , the partitioning of the intermediate (-1.0), would cancel one another leading to an over-all rate constant, k_h , which is insensitive to substituent effects. This is essentially what is found. This result can be rationalized in the following way. It has been shown that $k_h = k_1/((k_2/k_3) + 1)$. In the reactions investigated here k_2/k_3 varies from 14.7 for *p*-chloroacetanilide to 4.3 for *p*-methoxyacetanilide. Thus, k_2/k_3 is considerably larger than unity in all reactions. Therefore $k_h \cong k_1/(k_2/k_3)$ or $\cong k_1(k_3/k_2)$. It has been theoretically derived^{15a} and experimentally verified^{15a,b} that when an over-all rate constant is the product of several individual rate constants, the Hammett ρ for the over-all reaction can be expressed as the sum of the ρ 's of the individual rate constants. In the present case one can therefore say that

$$\rho_h = \rho_1 + \rho_{3/2} \quad (6)$$

The data from the present experiments fit this equation well, the observed values being ρ_h , $+0.1$; ρ_1 , $+1.0$; and $\rho_{3/2}$, -1.0 .¹⁶

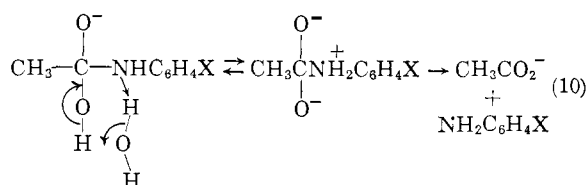
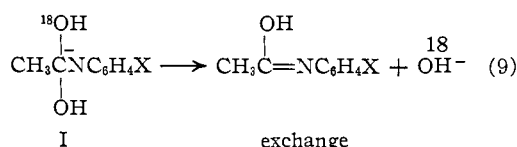
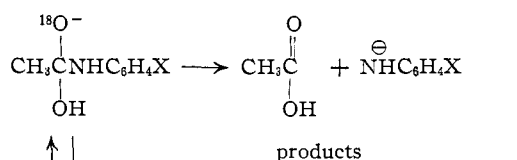
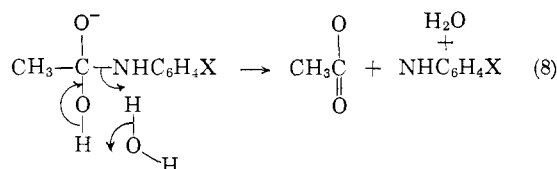
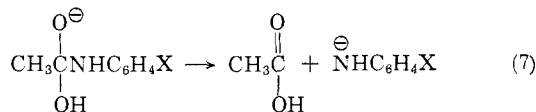
In order to explain the anomalous effect of substituents on the partitioning, let us consider some possible transformations of the tetrahedral addition intermediate produced from acetanilide and hydroxide ion. Listed below are four possible fates of the tetrahedral addition intermediate encompassing all of its important reactions. Equation 7 leads to the prediction that electron-withdrawing groups would facilitate product formation since they would stabilize the departing anion. Equation 8 leads to the prediction that electron-withdrawing groups would have little effect on k_h/k_{ex} since both bond-breaking and bond-making to nitrogen are involved and any substituent effects should cancel. Both eq. 7 and 8 therefore cannot explain the effect of substituents on the partitioning of the intermediate.

Equation 9 indicates that oxygen exchange can be facilitated, relative to hydrolysis, by electron-withdrawing substituents. This conclusion is based on the postulate that the exchange reaction proceeds through a symmetrical species in which the nitrogen atom possesses a negative charge, which of course will be stabilized by electron-withdrawing substituents.¹⁶ In all exchange reactions one must postulate the intermediacy of a symmetrical species, or the intermediacy of two species in equilibrium with one another which lead to an over-all symmetrical system. In this instance the symmetrical species I is postulated while in the other equations it is tacitly assumed that the two oxygen atoms are equivalent to one another through rapid proton transfer from oxygen to oxygen. Support is given to the explanation embodied in eq. 9 by

(15) (a) J. A. Leisten, *J. Chem. Soc.*, 765 (1959); (b) B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, **82**, 1773 (1960).

(16) It should be noted that the ρ 's given here, derived from the data shown in Fig. 3, apply to the hydrolysis where approximately 90% of the reaction proceeds through a process first order in hydroxide ion concentration ($[\text{OH}^-] = 0.239 M$). It is possible to extrapolate k_h , k_1 and k_3/k_2 to conditions where 100% of the reaction proceeds through a process first order in hydroxide ion concentration. Under these conditions the values obtained are ρ_h , 0.0; ρ_1 , $+1.0$ (k_1 can be shown to be independent of hydroxide ion concentration); and $\rho_{3/2}$, -1.1 . These data fit eq. 6 equally as well as those given above.

the observation that the alkaline hydrolysis of benzamide exhibits considerable oxygen exchange, while the alkaline hydrolysis of *N,N*-dimethylbenzamide exhibits no observable exchange.¹⁷ Since the latter compound contains no proton on nitrogen, the formation of a negatively-charged



intermediate leading to exchange would be impossible. Therefore eq. 9 will explain the effect of substituents on the partitioning of the tetrahedral intermediate.

Equation 10 will also explain the fact that electron-donating groups facilitate product formation from the tetrahedral intermediate. This process involves the equilibrium formation of a dipolar ion followed by breakdown to products. Since the position of the equilibrium of dipolar ion formation depends essentially on the basicity of the nitrogen atom of the anilide, dipolar ion formation would be expected to be favored by electron-donating substituents. Assuming that the further decomposition to products is rapid and thus not subject to substituent effects, this mechanism predicts the observed behavior.

Differentiation between mechanisms 9 and 10 is difficult. For example, eq. 10, as well as eq. 9, will explain the fact that no oxygen exchange occurs in the hydrolysis of *N,N*-dimethylbenzamide although there is considerable exchange with benzamide; the formation of the dipolar ion in

the former case should be enhanced over the latter case leading to greater product formation. However, only eq. 10 will explain the solvent effects observed in the alkaline hydrolysis of benzamide. In dioxane-water solutions it was found that as the percentage of water decreased, the ratio k_h/k_{ex} decreased, with k_h decreasing faster than k_{ex} .² A decrease in solvent polarity should decrease the fraction of the tetrahedral intermediate in the dipolar ion form and lead to a decrease in k_h relative to k_{ex} and thus a decrease in the ratio k_h/k_{ex} . Furthermore, eq. 10 utilizes the amine group as a base while eq. 9 utilizes the amine group as an acid. The former appears to be a more reasonable possibility, and therefore at this time eq. 10 is favored as the explanation for the effect of substituents on k_3/k_2 .

In conclusion it is postulated that the breakdown of the tetrahedral intermediate of an anilide or amide, or other compound which contains a group whose anion is extremely unstable in water, must proceed first through protonation of that group, in this instance by dipolar ion formation, followed by collapse to products. The result is probably different in kind from that of ester hydrolysis where the alkoxide group can depart from the tetrahedral intermediate as the anion: that is, the alkoxide ion does not need to be protonated before departure.¹⁸ In the saponification of substituted phenyl acetates, for example, where strict adherence to a Hammett relationship is found (slope of about 1.1),¹⁹ it is possible that both the formation of the tetrahedral intermediate and its breakdown to products are facilitated by electron-withdrawing groups. However, the ρ determined for the phenyl acetates is undoubtedly the ρ only for the formation of tetrahedral intermediate, since a phenyl ester has been shown to give no observable exchange,²⁰ which means that k_2/k_3 is very small compared to one and that $k_h = k_1$. Therefore no direct information on the partitioning of the intermediate can be obtained. In the hydrolysis of anilides and similar compounds, however, substituent effects on both the formation and breakdown of the tetrahedral intermediate can be determined. The formation and breakdown of the intermediate are affected in completely different directions by substituents, leading to an over-all dependence on substituents which is very small.

The Complete Hydrolytic Process.—For the complete hydrolytic process involving both first- and second-order dependence on hydroxide ion we have written the generalized scheme in eq. 3 which leads to the rate constant for hydrolysis shown in brackets in eq. 4. Further, one can write an analogous scheme for the oxygen exchange accompanying such a hydrolysis; this is shown in eq. 11,²¹ where I_1' is the intermediate shown in eq. 10 and I_2 is $\text{CH}_3\text{C}(\text{O}^-)_2\text{NHC}_6\text{H}_4\text{X}$.

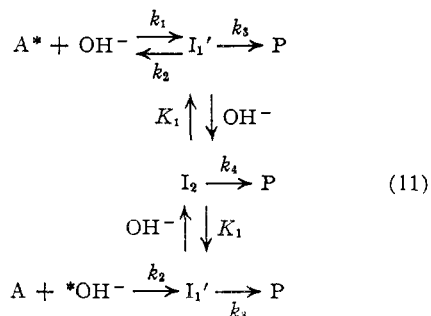
(18) See J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960).

(19) T. C. Bruice and M. F. Mayahi, *ibid.*, **82**, 3267 (1960).

(20) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1958).

(21) In eq. 11, 12 and 13, k_3 is assumed to be equal to K_2k_6 where K_2 is the equilibrium constant for the formation of the dipolar ion and k_6 is the rate constant of its decomposition.

(17) C. A. Bunton, personal communication.



The exchange rate constant derived from eq. 11 using the steady state approximation is shown in eq. 12 and the ratio k_h/k_{ex} is shown in eq. 13.

$$k_{ex} = \frac{k_1 k_2 (OH^-)}{2(k_2 + k_3 + k_4 K_1 (OH^-))} \quad (12)$$

$$k_h/k_{ex} = 2(k_3 + k_4 K_1 (OH^-))/k_2 \quad (13)$$

There is some ambiguity as to the representation of $K_1 k_4$ since this combination of an equilibrium and a rate step could be replaced by a rate step itself without the equilibrium. This, however, will not change the form of the equations: the only difference will be the replacement of the terms involving $K_1 k_4$ by k_5 .

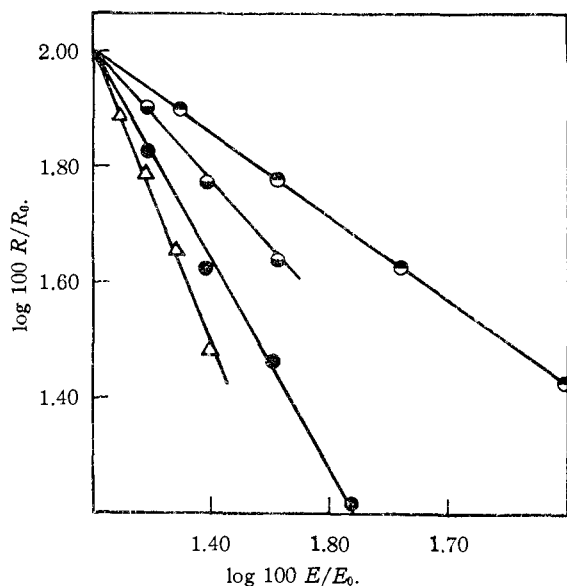


Fig. 4.—Oxygen exchange during the hydrolysis of substituted acetanilide in aqueous solution at 24.84° ($\mu = 0.957$, $[OH^-] = 0.957$): Δ , *p*-Cl; \bullet , *p*-H; \circ , *p*-CH₃; \ominus , *p*-CH₂O.

Two predictions can be made on the basis of eq. 12 and 13.²² One prediction is that k_h/k_{ex} should increase with increasing hydroxide ion concentration. The other prediction is that $k_{ex}/(OH^-)$ should decrease with base concentration. In order to test these predictions, oxygen exchange data have been obtained at $0.957 M$ sodium hydroxide, supplementing the oxygen exchange data at lower hydroxide ion concentration. At $0.957 M$ sodium

(22) One interesting consequence of eq. 12 and 13 is that k_1 can be shown to be equal to $(2k_{ex} + k_h)/(OH^-)$. Therefore it is possible to calculate k_1 irrespective of the hydroxide ion concentration used in the reaction. Values of k_1 obtained in this way from reactions carried out under low and high hydroxide ion concentration are indeed identical with one another.

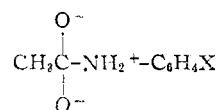
hydroxide, more of the reaction proceeds through the process second order in hydroxide ion, although by no means all of it. Figure 4 illustrates the oxygen exchange occurring in the reaction at $0.957 M$ sodium hydroxide and Table I summarizes the oxygen exchange data at both hydroxide ion concentrations. It is seen that both predictions made above are borne out by a comparison of the oxygen exchange results at $0.239 M$ and $0.957 M$ hydroxide ion. Thus the formulations given above are in agreement with all presently available data on these systems.

TABLE I
OXYGEN EXCHANGE DATA FOR THE BASIC HYDROLYSIS OF SUBSTITUTED ACETANILIDES^a

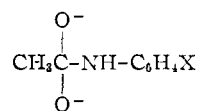
Substituent	k_h/k_{ex}	k_h , hr. ⁻¹	k_{ex} , hr. ⁻¹	$k_{ex}/(OH^-)$, l./mole hr.
Hydroxide ion = 0.239 M				
<i>p</i> -Cl	0.135	0.00729	0.0540	0.226
<i>p</i> -H	.216	.00650	.0301	.126
<i>p</i> -CH ₃	.332	.00589	.0177	.0740
<i>p</i> -CH ₂ O	.467	.00705	.0151	.0632
Hydroxide ion = 0.957 M				
<i>p</i> -Cl	0.208	0.0385	0.185	0.193
<i>p</i> -H	.284	.0341	.120	.125
<i>p</i> -CH ₃	.452	.0311	.0689	.0720
<i>p</i> -CH ₂ O	.697	.0362	.0519	.0542

^a $\mu = 0.957$, temp. $24.7 \pm 0.1^\circ$.

In the hydrolytic pathways involving both first-order and second-order dependence on hydroxide ion it has been postulated that intermediates involving two negative charges are formed. In the former pathway it is postulated that the dipolar ion



is formed and in the latter pathway it is postulated that the dianion



is formed. Thus the two processes postulated proceed on a parallel basis except for the protonation of the nitrogen in the former reaction which does not occur in the latter reaction. In both reactions the dianionic intermediate will decompose directly to a resonance-stabilized acetate ion. It has been postulated that the mechanisms of two other reactions, the basic hydrolysis of acetylacetone and the Cannizzaro reaction, involve dianions of similar structure.^{23,24} In the basic hydrolysis of both acetanilide and acetylacetone, one cannot distinguish between: (1) the formation of a dianionic intermediate in an equilibrium process from the monoanion and hydroxide ion; and (2) its kinetic equivalent in which hydroxide ion, in a rate-determining process, removes a proton from the

(23) R. G. Pearson and E. A. Mayerle, *J. Am. Chem. Soc.*, **73**, 926 (1951).

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

monoanion intermediate leading directly to products. In the above discussion process 1 has been implicitly favored for reasons of symmetry. However, a decision between processes 1 and 2 must wait until evidence concerning general basic or specific hydroxide ion catalysis of the step second order in hydroxide ion is available.

Acknowledgment.—The authors wish to express their appreciation to Dr. H. Taube of the University of Chicago through whose courtesy the mass spectrometer under AEC Contract At(11-1)-92 was made available, and acknowledge with pleasure valuable discussions with Dr. C. A. Bunton and Dr. G. A. Hamilton.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL., AND NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

The Concurrent Alkaline Hydrolysis and Isotopic Oxygen Exchange of a Series of *p*-Substituted Methyl Benzoates^{1,2}

BY MYRON L. BENDER³ AND ROBERT J. THOMAS

RECEIVED MAY 13, 1961

The kinetics of the concurrent alkaline hydrolysis and isotopic oxygen exchange of five *p*-substituted methyl benzoates have been determined in 33¹/₃% dioxane-water. The kinetics of hydrolysis precisely obey a Hammett relationship with a rho of +1.93. Contrary to predictions based on the previous mechanism of concurrent hydrolysis and exchange, the *p*-substituent has a large effect on the ratio k_h/k_{ex} , which varies from 30 for the *p*-NH₂ ester to 2.8 for the *p*-NO₂ ester. This result is rationalized by assuming 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. Estimates of the rates of these two processes indicate that this is a reasonable assumption, and that the previous hypothesis that proton transfer was kinetically insignificant may be incorrect.

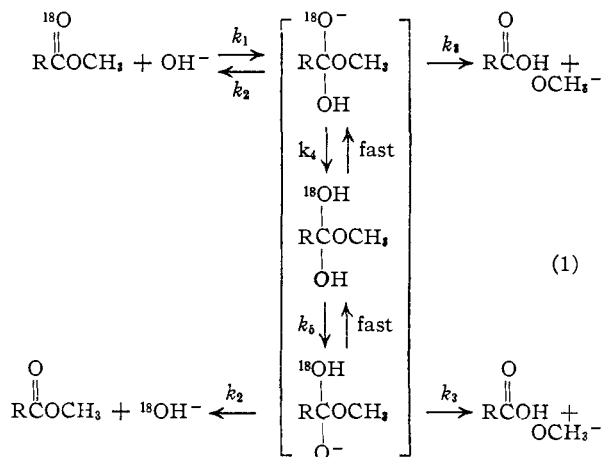
Introduction

Concurrent carbonyl oxygen exchange and hydrolysis have been demonstrated in the hydrolyses of a number of benzoate esters including methyl benzoate.^{4,5} This concurrent hydrolysis and exchange has been interpreted in terms of the partitioning of an unstable tetrahedral addition intermediate of the form RC(OH)₂OR. The magnitude of the carbonyl oxygen exchange which accompanies hydrolytic reactions of various 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 the electronic nature of the leaving group on the partitioning of the tetrahedral intermediate in the alkaline hydrolysis of a series of *p*-substituted acetanilides led to the postulation of a second intermediate, a dipolar ionic species. The present paper describes an investigation in which the electronic nature of the carboxylic acid group of an ester has been systematically varied in order to determine the effect of electronic donation or withdrawal from a different portion of the molecule on the partitioning of the tetrahedral intermediate.

If one were to make an *a priori* judgment on the outcome of the present experiments, the obvious prediction would be that the partitioning of the tetrahedral intermediate in the alkaline hydrolyses of a series of *p*-substituted methyl benzoates, as determined by the observation of the ratios of

k_h/k_{ex} , would be insensitive to the effect of substituents. This prediction is a natural outgrowth of the generalization enunciated by Hammett that structural variations in the B group of the reaction $A + BC \rightarrow AB + C$ lead to opposing effects in the bond-making and bond-breaking process of such a reaction and in the symmetrical case the two effects will completely cancel while in the general case the effects will be variable and unpredictable in sign, and small in magnitude.⁶

In the alkaline hydrolysis of a methyl ester it has been postulated⁴ on the basis of oxygen exchange evidence that the mechanism is



Using this mechanism one can show that the over-all hydrolytic rate constant, k_h , is equal to $k_1/((k_2/k_3) + 1)$ and further that $k_h/k_{ex} = 2k_3/k_2$. Thus the ratio of the partitioning of the tetrahedral intermediate to products or to reactants is directly measured by the ratio of hydrolysis to exchange

(1) This research was supported by grants from the National Science Foundation and the U. S. Atomic Energy Commission.

(2) Paper X 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**, 4183 (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).

(5) M. L. Bender, H. Matsui, R. J. Thomas and S. W. Tobey, *ibid.*, **83**, 4193 (1961).

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