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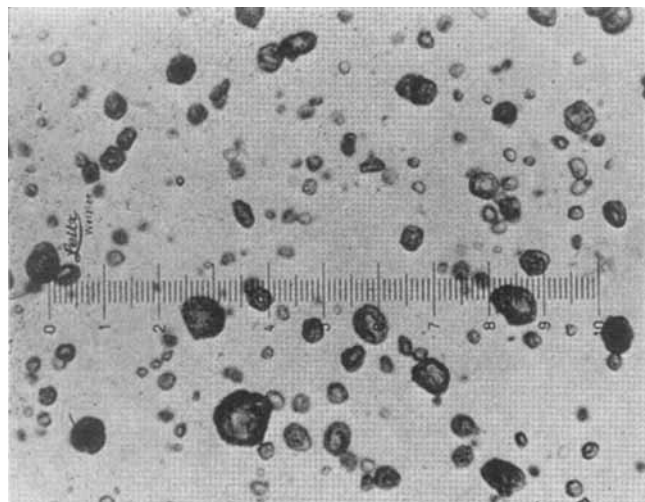
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**Figure 7**—An aqueous suspension of coated DMHB crystals after 1 year's storage at ambient conditions (magnification: 0-1 equals 63.9  $\mu$ ).

illustrates the value of having a choice of materials and processes which can be used to arrive at the best formulation prior to clinical testing. In this instance, the PCD proved to be a useful addition to equipment available in these laboratories for the formulation of a suspension having a prolonged *in vitro* release.

## Correlation and Prediction of Rates of Alkaline Hydrolysis of Some Benzoate Esters

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**Abstract** □ Rate constants have been determined for the alkaline hydrolysis of 36 *p*-substituted alkyl benzoates, and it is shown that these esters can be characterized on the basis of their rates of alkaline hydrolysis. Application of linear free-energy relationships allows calculation of alkaline hydrolysis rate constants for alkyl or aromatic *p*-substituted benzoate esters not included in this study. It is demonstrated that rates can be predicted for esters whether substituent variation is in the acyl or alkyl portion of the molecule by using the conventional Hammett treatment and the more recent alcohol dissociation model.

**Keyphrases** □ Benzoate esters—alkaline hydrolysis rates □ Alkaline hydrolysis rates—benzoate ester identification □ Linear free-energy relationships—alkaline hydrolysis rate prediction □ UV spectrophotometry—reaction monitoring

Earlier papers in this series (1-4) demonstrated that precise kinetic measurements can be a powerful tool in the identification of organic compounds. In addition, the large number of rate constants generated in these studies, under constant conditions, provides the necessary data for structure-reactivity relationships, mechanistic interpretations, *etc.* The classes of organic compounds previously considered were: alcohols [rates

of alkaline hydrolysis of their 3,5-dinitrobenzoate esters (1)], sugars [rates of oxime formation (2)], aliphatic amines [rates of cinnamoylation (3)], and aliphatic esters [rates of alkaline hydrolysis (4)]. The present study demonstrates that rates of alkaline hydrolysis can be used to identify aromatic esters and presents linear free-energy relationships to predict rates of alkaline hydrolysis for esters not included in the study.

## EXPERIMENTAL

**Chemicals**—Fisher certified acetonitrile was used without further purification after it was established that it was spectrally pure (from 220-300  $m\mu$ ) and that it had no anomalous effect on the rate of alkaline hydrolysis. All other chemicals were either analytical or reagent grade. Water was double distilled from acid permanganate in an all-glass distillation apparatus.

All esters were prepared according to procedures outlined by Shriner *et al.* (5) with slight modification. The acyl chloride was reacted with the appropriate alcohol by heating under reflux for 30 min. The reaction mixture was then taken up in chloroform and extracted with 5%  $\text{Na}_2\text{CO}_3$  followed by water and finally dried with  $\text{MgSO}_4$ . After removing the chloroform under vacuum, the ester remaining was purified by repeated recrystallization from water or from the alcohol representing the alkyl portion of the ester or, in the case of liquids, by vacuum distillation.

**Table I**—Second-Order Rate Constants for the Alkaline Hydrolysis of Some Benzoate Esters<sup>a</sup>

Ester	$k \times 10^4$ , l./msec.	Number of Determinations	$SD^b$
Methyl benzoate	6.08	2	0.05
Ethyl benzoate	1.98	2	0.02
<i>n</i> -Propyl benzoate	1.67	3	0.04
Isopropyl benzoate	0.319	2	0.05
<i>n</i> -Butyl benzoate	1.41	2	0.02
Isobutyl benzoate	1.18	3	0.07
Methyl <i>p</i> -nitrobenzoate	275.5	6	6.9
Ethyl <i>p</i> -nitrobenzoate	98.8	6	3.9
<i>n</i> -Propyl <i>p</i> -nitrobenzoate	76.0	5	1.8
Isopropyl <i>p</i> -nitrobenzoate	19.6	4	1.3
<i>n</i> -Butyl <i>p</i> -nitrobenzoate	63.4	3	0.8
Isobutyl <i>p</i> -nitrobenzoate	60.0	4	2.2
Methyl <i>p</i> -chlorobenzoate	19.1	4	0.45
Ethyl <i>p</i> -chlorobenzoate	6.51	3	0.39
<i>n</i> -Propyl <i>p</i> -chlorobenzoate	5.11	3	0.65
Isopropyl <i>p</i> -chlorobenzoate	1.21	2	0.02
<i>n</i> -Butyl <i>p</i> -chlorobenzoate	3.49	4	0.29
Isobutyl <i>p</i> -chlorobenzoate	3.36	3	0.08
Methyl <i>p</i> -methylbenzoate	2.65	4	0.20
Ethyl <i>p</i> -methylbenzoate	0.879	2	0.009
<i>n</i> -Propyl <i>p</i> -methylbenzoate	0.671	3	0.04
Isopropyl <i>p</i> -methylbenzoate	0.200	2	0.02
<i>n</i> -Butyl <i>p</i> -methylbenzoate	0.568	2	0.03
Isobutyl <i>p</i> -methylbenzoate	0.449	2	0.009
Methyl <i>p</i> -fluorobenzoate	12.1	3	0.2
Ethyl <i>p</i> -fluorobenzoate	4.05	3	0.08
<i>n</i> -Propyl <i>p</i> -fluorobenzoate	2.65	3	0.07
Isopropyl <i>p</i> -fluorobenzoate	0.623	3	0.04
<i>n</i> -Butyl <i>p</i> -fluorobenzoate	2.44	3	0.06
Isobutyl <i>p</i> -fluorobenzoate	1.90	3	0.24
Methyl <i>p</i> -cyanobenzoate	195.0	4	2.4
Ethyl <i>p</i> -cyanobenzoate	79.7	5	1.50
<i>n</i> -Propyl <i>p</i> -cyanobenzoate	52.6	3	0.34
Isopropyl <i>p</i> -cyanobenzoate	12.6	5	0.24
<i>n</i> -Butyl <i>p</i> -cyanobenzoate	41.9	3	1.16
Isobutyl <i>p</i> -cyanobenzoate	39.4	4	1.50

<sup>a</sup> In 50% v/v acetonitrile–0.02 *M* phosphate buffer at 25°. <sup>b</sup> Standard deviation.

**Apparatus**—pH Measurements and adjustments were made on a Corning model 12 pH meter with an expanded scale using a Beckman type E3 wide-range glass electrode. The pH meter and electrode system was standardized against a phosphate buffer as described by Bates (6).

Water bath temperatures were maintained to 0.1° with Sargent Thermonitor electronic relays. The progress of the reactions was followed on either a Cary model 11 or 14 recording spectrophotometer with thermostated cell compartments.

### PROCEDURE

**Solvent System**—Fifty milliliters of acetonitrile was added to an equal volume of a 0.02 *M* dibasic phosphate buffer, and the resulting solution was brought to the appropriate pH with a few drops of concentrated NaOH solution. The acetonitrile–phosphate buffer solution gives a volume somewhat less than 100 ml. This solution was used for all kinetic determinations.

**Continuous Spectrophotometric Procedure**—For reactions that had sufficiently rapid rates so that they could be followed directly in the spectrophotometer, the following procedure was used. After equilibrating the solvent system to 25°, 3 ml. of solvent was thoroughly mixed with 50  $\mu$ l. of a  $1 \times 10^{-2}$  *M* ester in acetonitrile solution in a 1-cm. photometer cell. The reaction progress was monitored by following the disappearance of ester at an appropriate wavelength, benzoates at 242  $m\mu$ , *p*-methyl benzoates at 250  $m\mu$ , *p*-chlorobenzoates at 254  $m\mu$ , *p*-fluorobenzoates at 244  $m\mu$ , *p*-cyanobenzoates at 250  $m\mu$ , and by the appearance of acid anion at 290  $m\mu$  in the *p*-nitrobenzoate case.

**Discontinuous Spectrophotometric Procedure**—For esters with inconveniently long rates of reaction, the following sampling pro-

cedure was used. One hundred milliliters of the buffer solution was prepared and brought to the appropriate pH. Two milliliters of  $1 \times 10^{-2}$  *M* ester in acetonitrile solution was added to the buffer solution, and the resulting mixture was placed in 5-ml. volumetric flasks which were stored in a 25° water bath. At appropriate time intervals the contents of two of the volumetric flasks were used to determine the concentration of remaining ester or acid anion. This sampling procedure was necessary due to the volatility of acetonitrile.

**Data Treatment**—All experiments were carried out with a large excess of hydroxide ion and thus pseudo-first-order kinetics were observed. Pseudo-first-order rate constants were obtained in the usual manner and were converted to second-order rate constants by dividing by the hydroxide-ion activity.

### RESULTS

Second-order rate constants were calculated for the various esters and are presented, together with standard deviations, in Table I. At least two rate determinations were made for each ester, and these were carried out at more than one pH value to ensure that the reactions were first-order in hydroxide ion. The pH range employed for these esters in this solvent system was from 12 to 13.4. Above pH 13.4, phosphate precipitates; below pH 12, the rates are inconveniently slow. The buffer capacity of the solvent system, for concentrations of ester employed in this study, was satisfactory from pH 11 to 13.4.

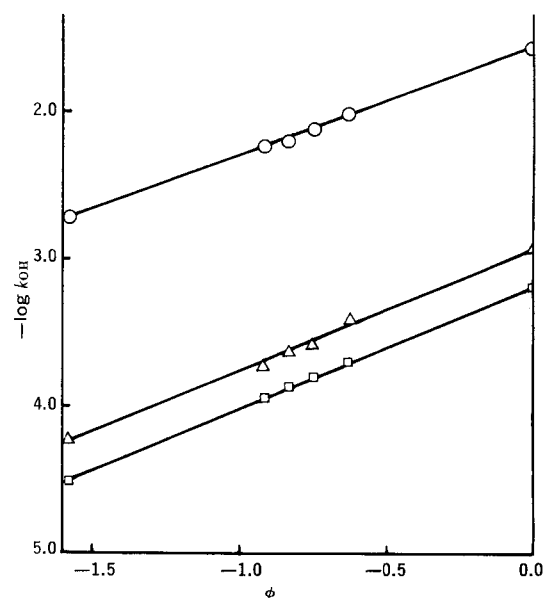
Correlations of structure and reactivity were made using the Hammett relationship (7)

$$\log \frac{k}{k_0} = \sigma \rho \quad (\text{Eq. 1})$$

and a modified form of the Hammett equation (8)

$$\log \frac{k}{k_0} = \phi M \quad (\text{Eq. 2})$$

For variation in the acyl portion of the ester molecule, substituent constants ( $\sigma$  values) were obtained from the literature (9) and were plotted against log rate constants.<sup>1</sup> For substituent variation in the alkyl portion of the ester molecule,  $\phi$  values (8) were plotted against log rate constants. Representative plots for both of these treatments are shown in Figs. 1 and 2. Slopes, standard deviations, and correla-



**Figure 1**—Plot of the second-order rate constants for alkaline hydrolysis of alkyl-substituted benzoate esters against  $\phi$  values. Key: O, *p*-nitro benzoates;  $\Delta$ , *p*-fluoro benzoates, and  $\square$ , benzoates.

<sup>1</sup> The substituent constant for the *p*-fluoro group is reported to be 0.06 (9) or 0.17 (10). Although neither value gave good correlations, the 0.06  $\sigma$  value was used in this study.

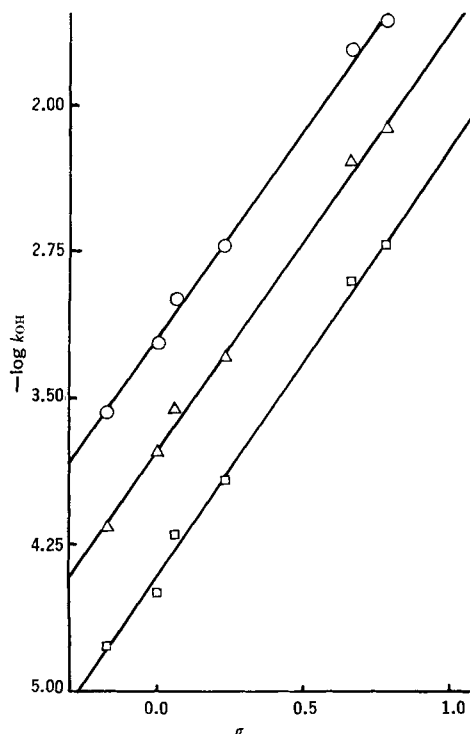


Figure 2—Plot of the second-order rate constants for alkaline hydrolysis of *p*-substituted alkyl benzoate esters against Hammett's polar substituent constants. Key: ○, methyl benzoate esters; △, *n*-propyl benzoate esters, and □, isopropyl benzoate esters.

tion coefficients for these plots and the remaining esters are shown in Table II.

## DISCUSSION

It is apparent from Table I that the rate of alkaline hydrolysis is a useful way to identify these aromatic esters. The ratio of the largest to the smallest rate constants for these 36 esters is about 1600; within a given series the constants are sufficiently different so that any ester is easily differentiated from a similar member. It is also clear from the reported rates that for some esters the rates are prohibitively slow, and this is obviously undesirable. However, sufficient rate data are presented to calculate the rates for a large number of esters. For many of these esters, this procedure will be a rapid, sensitive method which will be useful for characterization.

For esters not included in this study, it is possible to calculate the rate of alkaline hydrolysis under the specific conditions of this study (solvent composition and temperature) by employing linear free-energy relationships. For substituent variation in the acyl component of the ester molecule, the Hammett equation has had great success in correlating rates and structural modifications. Table II, Part 2, shows the excellent results that are obtained for the ester data generated in this study, using this procedure. Note that all of the correlation coefficients are better than 0.994, which is excellent. For changes in the alkyl portion of the molecule, the recently reported  $\phi$  values can be correlated with reaction rates. The results of this treatment are shown in Table II, Part 1. The correlation coefficients for this treatment are also excellent. Using both the Hammett relationship, which uses the dissociation of aromatic acids as the model process, and the  $\phi$  values, which are based on the dissociation of alcohols as the model process, it is possible to predict the rate of alkaline hydrolysis for any ester where the  $\sigma$  value (the acyl component) and  $\phi$  value (the alkyl component) have been determined.

Table II—Correlation of Relative Reaction Rates ( $\log k/k_0$ ) with Substituent Constants for Some Aromatic Esters

Ester Series	$M^b$	$SD^c$	$R^d$
<b>Part 1 Substituent Variations in the Alkyl Component<sup>e</sup></b>			
<i>p</i> -Methyl benzoates	0.772	0.030	0.997
Benzoates	0.816	0.023	0.999
<i>p</i> -Fluoro benzoates	0.832	0.039	0.997
<i>p</i> -Chloro benzoates	0.776	0.051	0.994
<i>p</i> -Cyano benzoates	0.771	0.046	0.995
<i>p</i> -Nitro benzoates	0.734	0.018	0.999
<b>Part 2 Substituent Variations in the Acyl Component<sup>e</sup></b>			
Ester Series	$\rho^f$	$SD^c$	$R^d$
Methyl benzoates	2.138	0.079	0.996
Ethyl benzoates	2.213	0.093	0.995
Propyl benzoates	2.184	0.049	0.999
Isopropyl benzoates	2.233	0.061	0.998
Butyl benzoates	2.158	0.077	0.996
Isobutyl benzoates	2.243	0.055	0.998

<sup>a</sup> The alkyl substituents for all series in this group were methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, and isobutyl. <sup>b</sup>  $M$  is the least-squares fitted slope of a  $\log$  (rate constant) vs.  $\phi$  plot. <sup>c</sup> Standard deviation of points from the line. <sup>d</sup> Correlation coefficient for the line. <sup>e</sup> The acyl substituents for all series in this group were *p*-methyl, *p*-hydrogen, *p*-fluoro, *p*-chloro, *p*-cyano, and *p*-nitro. <sup>f</sup>  $\rho$  is the least-squares fitted slope of a  $\log$  (rate constant) vs.  $\sigma$  plot.

This is accomplished by simple extrapolation or interpolation of the log rate constant versus substituent constant plot.

Other procedures are available to predict rates of hydrolysis for esters when structure variations are made in both the acyl and alkyl portions of the ester molecule (11). These procedures are empirical in nature and have undesirable features associated with them. A thorough discussion of the two procedures, as well as the mechanistic significance of the slopes generated in this study, will be the subject of another publication.

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