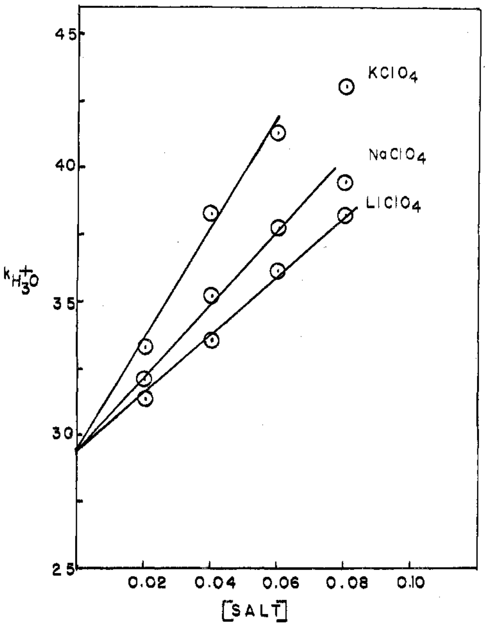

Figure 1. Plot of $k_{H_3^+O}$ vs. concentration of salt for $LiClO_4$, $NaClO_4$, and $KClO_4$ for the hydrolysis of benzaldehyde dimethyl acetal in water at 25.39 °C. The lines were placed by least squares.

spectively.[3] All rate constants were calculated by the method of least squares. One may also calculate the reverse rate constants, k_2, from this same data if desired,[3] but these values are not reported.

Results and Discussion

The influence of the concentration of sodium perchlorate (0.0–0.10 M) has been studied on the rates of formation of the dimethyl acetals of *p*-anisaldehyde, *p*-tolualdehyde, benzaldehyde, and *p*-bromobenzaldehyde. The reactions were conducted in 95% methanol–5% water at 25.39 °C with perchloric acid catalyst. The results are summarized in Table I. The kinetic salt effect is summarized by the expression

$$k_{H_3^+O} = k_0 + b[\text{salt}] \qquad (3)$$

We have reported[3] that the rates of acetal formation increase as the electron-donating capability of the para substituents increase. Paralleling this rate–structure effect is the kinetic salt effect which the slope term, *b*, represents. The values of *b* given in Table I are seen to increase as the electon-donating capability of the para substituent increases. It is apparent that the methoxy group has a much greater slope than the bromo group and presumably the slope would be zero for a substituent having a zero rate.

Given the form of the kinetic salt effect for this reaction, are the relative rates for various substituents the same as long as the rates are measured at the same salt concentration? The results show a positive answer to this question. This fact may be seen by taking ratios of the rate expressions (eq 3) for various substituents. The results show an average *q* value of 2.60 and represent the slope of a line obtained by plotting the *b* terms vs. the intercepts for the para-substituted benzaldehydes. On this basis one may be confident of interpretations of relative rates for substituents providing they are made at the same electrolyte concentration.

Most results of kinetic salt studies of this type have been performed in water and usually the data have been treated by a log *k* vs. [salt].[5,6] It seemed possible that the effects we observed reflected a methanol–water–salt interaction rather than a reactant–salt interaction. Because of this possibility and because we had observed what to us seemed to be a specific salt effect in methanol–water we extended this study to the hydrolysis of benzaldehyde dimethyl acetal in water. The reaction was conducted at 25.39 °C with perchloric acid catalyst ($\sim 10^{-5}$ M) used with various amounts of lithium, sodium, or potassium perchlorates.

The preliminary results of the hydrolysis reaction in water are summarized in Figure 1. The plots of k_{H_3O} vs. salt concentration are satisfactorily linear with corrections coefficients of $r = 0.986$ for $KClO_4$, $r = 0.995$ for $NaClO_4$, and $r = 0.997$ for $LiClO_4$. The kinetic salt effect increases in the order Li < Na < K. These results show that the salt effect observed for acetal hydrolysis in water is of the same kind as we observed for acetal formation in methanol–water.

The 0.08 M salt values for $KClO_4$ and $NaClO_4$ are considerably off the line (although these values were included in the least-squares correlations). This deviation occurs because of a significant change in slope which is observed at about 0.1 M salt for all salts studied to date. The salt effects observed are ion specific and while the results presented demonstrate specific cation effects, specific anion effects have also been observed. Details of this kinetic salt effect for acetal hydrolysis in water are to be reported in more detail. We would note only that the results are of the same form Winstein has observed for the solvolysis of arenesulfonates.[7]

Registry No.—$LiClO_4$, 7791-03-9; $NaClO_4$, 7601-89-0; $KClO_4$, 7778-74-7; benzaldehyde dimethyl acetal, 1125-88-8.

References and Notes

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Acidity Constants of Some 5-Substituted 3-Furoic Acids[1]

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A great number of examples of the application of Hammett's equation to series of reactions of several aromatic heterocyclic systems are found in the literature.[2] In the furanic system, in particular, owing to the difficulty found in the synthesis of β-substituted derivatives, the use of this equation has been restricted almost exclusively to those systems in which the relation between the substituent R and the reacting side chain Y is of the 5-R-2-Y type.

In order to extend the observation made on the transmission of the substituent's effect to the "nonconjugated" 5-R-3-Y relationship in the furanic system, a series of 5-substituted 3-furoic acids were prepared and their pK_a values were determined and correlated with the corresponding Hammett substituent constants.

Experimental Section

The ^1H NMR spectra were determined on a Varian T-60 instrument using Me_4Si as an internal reference. The ir spectra were recorded using a Perkin-Elmer 337 spectrophotometer. All melting and boiling points are uncorrected.

Table I. ^{1}H NMR Chemical Shifts[a] and Coupling Constants of 5-Substituted 3-Furoic Acids

			δ, ppm, and multiplicity				
Registry no.	Compd	Solvent	H2	H4	H5	CO_2H	J, Hz
488-93-7	Unsubstituted[b]	$CDCl_3$	8.13 (q)	6.80 (t)	7.47 (q)	10.67 (s)	$J_{45} = 1.9$; $J_{25} = 1.6$; $J_{24} = 0.8$
4282-28-4	5-CO_2H	$(CD_3)_2CO$	8.38 (d)	7.45 (d)		8.97 (s)	$J_{24} = 0.9$
58832-36-3	5-Br	$CDCl_3$	8.07 (d)	6.71 (d)		9.87 (s)	$J_{24} = 1.2$
770-07-0	5-NO_2	$(CD_3)_2CO$	8.47 (d)	7.72 (d)		10.90 (s)	$J_{24} = 1.1$

[a] From internal Me_4Si. [b] Reported[8] δ 8.12, 6.78, 7.45, 11.60 ppm.

Table IV. Apparent Ionization Constants, pK_a', and Thermodynamic Ionization Constants, pK_a, at 25.0 ± 0.1 °C of 5-Substituted 3-Furoic Acids in Water Solution

Compd	I_m	pK_a'	s[a]	$-\log \gamma_i$	pK_a
3-Furoic acid	0.005	3.99[b]	0.01	0.04	4.03
5-Bromo-3-furoic acid	0.005	3.64	0.01	0.04	3.68
5-Nitro-3-furoic acid	0.005	3.04	0.01	0.04	3.08
2,5-Furandicarboxylic acid					
2 position	0.006	2.65	0.01	0.041	2.69
4 position	0.020	3.96	0.01	0.056	4.13

[a] Standard deviation. [b] Reported[17] 3.95.

2,4-Furandicarboxylic acid was prepared through the following sequence of reactions. Coumalic acid was prepared from malic acid.[3] The coumalic acid was converted into coumalyl chloride according to Fried and Elderfield's procedure,[4] using the modification proposed by Wiley and Knabeschuh.[5] The coumalyl chloride was converted into methyl coumalate.[5] The methyl coumalate was converted into methyl bromocoumalate[6] and then into 2,4-furandicarboxylic acid.[6] Ir spectrum (KBr) showed peaks at 1694 (ν_{CO}), 1586 and 1563 (ν_{ring}), 1155 (β_{CH}), 870 (β_{ring}), and 765 cm^{-1} (δ_{CH}).

3-Furoic acid was prepared from 2,4-furandicarboxylic acid by Reichstein and Zschokke's method.[7] Ir spectrum (KBr) showed peaks at 1670 (ν_{CO}), 1564 and 1510 (ν_{ring}), 1155 (β_{CH}), 876 (β_{ring}), and 750 cm^{-1} (δ_{CH}).

5-Bromo-3-furoic acid was prepared by the following method. 3-Furoic acid (2.38 g, 0.02 mol) was added to a solution of 6.4 g (0.02 mol) of pyridinium hydrobromide perbromide[8] in 10 ml of acetic acid. The reaction mixture was heated to 40–45 °C during 2 h, while the hydrogen bromide formed was swept by a stream of nitrogen. Next, the solvent was evaporated under reduced pressure, and the remaining solid was suspended in water, filtered, dried, and sublimated under reduced pressure to give a 55% yield of a product with mp 138–139 °C (reported[6] 130 °C). Ir spectrum (KBr) showed peaks at 1670 (ν_{CO}), 155 and 1510 (ν_{ring}), 1130 (β_{CH}), 854 (β_{ring}), and 755 cm^{-1} (γ_{CH}).

5-Nitro-3-furoic acid was prepared as described below. Nitric acid (70%), 9 g (0.10 mol), was added during a 2-min period to 60 ml of acetic anhydride, the temperature being held at 30–35 °C. The solution was then chilled to −15 °C, after which were added 2 drops of concentrated sulfuric acid and 5.6 g (0.05 mol) of 5-furoic acid. The temperature of the solution was allowed to rise to 0 °C and the solution was stirred at this temperature for 15 min. Water was added and the solution was stirred until the hydrolysis of the acetic anhydride was complete, then extracted with ether. The ethereal solution was washed with water and dried, and the ether removed by distillation. The residual oil mixed with an equal volume of pyridine (violent reaction), cooled, acidified with a 50% hydrochloric acid solution, and extracted with ether. The ethereal solution was washed with water and dried, and the ether evaporated. The remaining solid was recrystallized from water, giving a 60% yield of a product of mp 136–137 °C (reported[6] 138 °C). Ir spectrum (KBr) showed peaks at 1670 (ν_{CO}), 880 (β_{ring}), and 761 cm^{-1} (δ_{CH}).

All the substances prepared were characterized by ^{1}H NMR (Table I).

pK_a Determinations. The apparent acidity constants, pK_a', of 3-furoic acid, 5-bromo-3-furoic acid, and 5-nitro-3-furoic acid were measured at 25.0 ± 0.1 °C, in water, by sequential titration of 5.0 × 10^{-4} mol of the acids dissolved in 47.5 ml of ion-free water, with 10 amounts of 0.1000 M carbonate-free potassium hydroxide solution each 0.1 equiv. After each addition the pH was measured with a Methron Herissau Compensator E 388 pH meter, equipped with a combined glass electrode, with silver–silver chloride internal reference, in an apparatus as described by Albert and Serjeant.[9] The instrument was calibrated against standard buffer solution at pH 2.00 and 6.00. The standardization of the instrument was rechecked after each determination, and in no case was the drift greater than 0.02 pH units. The temperature drifts during measurements were less than 0.1 °C. The apparente pK_a' values (Table II, supplementary material) were obtained from eq 1

$$\mathrm{p}K_a' = \mathrm{pH} + \log \frac{C_{AH} - a_{H^+}}{C_{A^-} + a_{H^+}} \qquad (1)$$

where C_{AH} and C_{A^-} are the stoichiometric concentration of the acid and its conjugated base, respectively.

The apparent acidity constant, pK_a', of 2,4-furandicarboxylic acid was measured at 25.0 ± 0.1 °C, in water, by sequential titration of 5.0 × 10^{-4} mol of the acid dissolved in 42.5 ml of ion-free water, with 20 amounts of 0.1000 M carbonate-free potassium hydroxide solution, each 0.05 equiv. The pH measurements were performed as above. The apparent pK_a' was obtained with the application of the Noyes method[10]

$$K'_{a1} = \frac{Y_1Z_1 - Y_2Z_1}{X_1Z_2 - X_2Z_1} \text{ and } K'_{a2} = \frac{X_1Z_2 - X_2Z_1}{Y_1Z_2 - Y_2Z_1} \qquad (2)$$

where $X = a_{H^+}(B - C + a_{H^+})$, $Y = 2C - (B + a_{H^+})$, $Z = (a_{H^+})^2(B + a_{H^+})$; C is the total concentration of the acid being titrated; B is the concentration of the alkali added.

For readings obtained with less than 1 equiv of the titrant the corresponding values are X_1, Y_1, and Z_1, whereas X_2, Y_2, and Z_2 refer to readings obtained with more than 1 equiv of titrant. Pairs of readings were selected symmetrically from either side of the midpoint (Table III, supplementary material).

Results and Discussion

The apparent acidity constants, pK_a', of 3-furoic acid, 5-bromo-3-furoic acid, 5-nitro-3-furoic acid, and 2,4-furandicarboxylic acid were determined at 25.0 ± 0.1 °C, in aqueous solution, by potentiometric titration, using the technique described by Albert and Serjeant.[9]

The pK_a' values shown in Table IV were calculated using nine points of the titration curve, between the limit of 10 and 90% of ionization. Equation 1 was employed in the calculation of the pK_a' values of the monobasic acids.

As was expected, the application of this calculation method to the data obtained from the titration of the dibasic acid did not yield good results, since the difference between the pK_a' values of the ionizing group is smaller than 2.7 pH units, thus causing the titration of one group to begin before that of the other group has been completed. Quite satisfactory results were obtained by applying the Noyes method[10] for separation of the overlapping pK_a' values (see Table IV). Since 2-furoic acid ($pK_a = 3.12^{11}$) is stronger than 3-furoic acid ($pK_a = 3.99^{11}$), we attributed the determined $pK_a' = 2.65$ to carboxyl group in position 2, and the $pK_a' = 3.96$ to the carboxyl group in position 4 of the 2,4-furandicarboxylic acid.

The thermodynamic pK_a for the 3-furoic acid, 5-bromo-3-furoic acid, and 5-nitro-3-furoic acid and the stronger group of the dibasic acid were calculated from the equation

$$pK_a = pK_a' - \log \gamma_i \qquad (3)$$

and using the Debye–Hückel limiting law to define the activity coefficient, γ_i, and the value of the ionic strength at the midpoint of the titration. The thermodynamic pK_a becomes $pK_a' + 0.04$ (see Table IV).

The thermodynamic pK_a of the weaker group of the 2,4-furandicarboxylic acid was calculated from the equation

$$pK_a = pK_a' - 3 \log \gamma_i \qquad (4)$$

The activity coefficient was calculated from the equation

$$-\log \gamma_i = \frac{A\sqrt{I_m}}{1 - Ba_i\sqrt{I_m}} \qquad (5)$$

Using the values of the constants A and B,[12] the value of the ionic size parameter,[13] and the value of the ionic strength of the solution, I_m, at the semineutralization, the thermodynamic pK_a becomes $pK'_{a2} + 0.17$ (see Table IV).

We have correlated, by multiple linear regression analysis,[14] the acidity constants values of the 5-substituted 3-furoic acids to the corresponding substituent constants values σ_m and σ_p, employing values determined by McDaniel and Brown.[15]

With the σ_m values the slope ρ of the regression line is 1.25 and the correlation coefficient is 0.983; with the σ_p values ρ is 1.28 and the correlation coefficient is 0.990. It is noteworthy that 5-substituted 3-furoic acids correlate well with both meta and para substituent constants.

The ratio between the value of ρ obtained and the corresponding values for the benzene system agrees with those found for the 2-R-5-Y system[2,16] and reinforces the conclusion that the transmission of the substituent's effect is greater in the furan ring than in the benzene ring.

Supplementary Material Available. Tables II and III that report full determination of the apparent acidity constant data for the 5-substituted 3-furoic acids (2 pages). Ordering information is given on any current masthead page.

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A Convenient Synthesis of *N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine

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In peptide synthesis, especially using the solid-phase method, *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine has proved to be a useful intermediate to incorporate serine into a synthetic peptide.[1] Although several methods are currently available for the preparation of the *O*-benzyl derivative, they are laborious and not profitable for commercial exploitation. *O*-Benzyl-DL-serine was prepared by Okawa[2] via bromination of methyl acrylate. Resolution into the L isomer was achieved by hydrolysis of the *N*-acetyl derivative with the acylase.[3] In addition, *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine was prepared by Hruby and Ehler[4] via benzylation of *N-tert*-butyloxycarbonyl-L-serine in sodium–liquid ammonia at −30 °C. Isolation of the desired product was performed by use of column chromatography. This paper is concerned with the development of a more convenient synthetic method starting from L-serine.

N-tert-Butyloxycarbonyl-*O*-benzyl-L-serine was obtained directly from the readily available *N-tert*-butyloxycarbonyl-L-serine by treatment of the latter compound, in dimethylformamide at room temperature, with 2 molar equiv of sodium hydride and 1 molar equiv of benzyl bromide. Purified *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine was obtained in 57% yield as its cyclohexylammonium salt after recrystallization from ethyl acetate. The method described here is suitable for large-scale preparation because of its high efficiency, procedural simplicity, and mildness of reaction conditions.

When the same procedure was applied to the preparation of the *O*-benzyl-L-threonine derivative, the yield of the compound was low as revealed by thin layer chromatography. By use of column chromatography *N-tert*-butyloxycarbonyl-*O*-benzyl-L-threonine was isolated in 14% yield.

Experimental Section[5]

***N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine Cyclohexylammonium salt.** To a solution of *N-tert*-butyloxycarbonyl-L-serine[6] (2.05 g, 10 mmol) in dimethylformamide (50 ml) was added sodium hydride (65%) (820 mg, 22 mmol) at 0 °C. After the evolution of hydrogen gas ceased, the freshly distilled benzyl bromide (1.88 g, 11 mmol) was added to the solution. The reaction mixture was stirred at 25–30 °C for 5 h to give a clear solution. The solvent was then removed under reduced pressure below 40 °C. The residue was dissolved in water (50 ml) and the solution was extracted with ether (two 20-ml portions). The aqueous phase was acidified to pH 3.5 with 3 N HCl, and extracted with ethyl acetate (five 20-ml portions). The combined organic layers were washed with water and dried over magnesium sulfate. The ethyl acetate was removed under reduced pressure to give a colorless oil. The oil was then dissolved in ether (30 ml) and cyclohexylamine (0.9 g) was added to the solution. A precipitate formed and was collected by filtration. The solid was washed well with ether. Recrystallization from ethyl acetate yielded the title compound (2.2 g, 57%): mp 159–160 °C; $[\alpha]^{25}D$ +29.0° (*c* 1, methanol) [authentic sample prepared by the known method,[6] mp 159–160 °C; $[\alpha]^{25}D$ +29.8° (*c* 1, methanol)].

Anal. Calcd for $C_{15}H_{21}NO_5{\cdot}C_6H_{13}N$: C, 63.93; H, 8.69; N, 7.10. Found: C, 63.76; H, 8.54; N, 6.89.

Optical Purity of *O*-Benzyl-L-serine. One gram of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine prepared by the above procedure was dissolved in 2 N HCl–AcOH (5 ml). After 1 h at room temperature, the solvent was evaporated under reduced pressure below 35 °C to yield crystals. The crystals showed the same optical rotations as a sample of *O*-benzyl-L-serine hydrochloride prepared by the method previously reported,[3] $[\alpha]^{25}D$ +7.4° (*c* 2, 1 N HCl).