

## Linear Free Energy *ortho*-Correlations in the Thiophen Series. Part IV.<sup>1</sup> Kinetics of Alkaline Hydrolysis of Some Methyl 3-Substituted Thiophen- 2-carboxylates in Aqueous Methanol

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The rate constants for the alkaline hydrolysis of some methyl 3-substituted thiophen-2-carboxylates (I) (substituents OMe, Me, SMe, H, I, Br, SOMe, and SO<sub>2</sub>Me) in methanol-water (80% v/v) have been determined. The logarithms of the rate constants give an excellent straight line when plotted against the p*K*<sub>a</sub> values of the corresponding acids (slope 1.91) and obey an equation of the Yukawa-Tsuno type ( $\rho + 2.77, r^+ 0.44, R 0.996$ ), confirming the marked difference in behaviour between *ortho*-like substituted thiophen and benzene derivatives.

As stated by Hammett in his classical studies on linear free energy relationships (LFERs), 'the points for aliphatic compounds and *ortho*-substituted benzene deriva-

<sup>1</sup> Part III, D. Spinelli, G. Consiglio, and R. Noto, *J.C.S. Perkin II*, 1976, 1495.

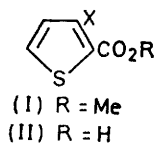
<sup>2</sup> (a) L. P. Hammett, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1940, 1st edn., pp. 184 *et seq.*; 1970, 2nd edn., pp. 347 *et seq.*; (b) O. Exner in 'Advances in Linear Free Energy Relationships,' eds. N. B. Chapman and J. Shorter, Plenum Press, London, 1972, pp. 2 *et seq.*

tives 'fail' to adhere to the line defined by the *meta*- and *para*-substituted derivatives.'<sup>2a</sup> In particular, there is no correlation<sup>2,3</sup> between p*K*<sub>a</sub> values of *ortho*-substituted benzoic acids and logarithms of the rate constants for alkaline or acidic hydrolysis of the corresponding esters.

<sup>3</sup> K. Kindler, *Annalen*, 1926, **450**, 1; 1928, **464**, 278; D. P. Evans, J. J. Gordon, and H. B. Watson, *J. Chem. Soc.*, 1937, 1430.

This observation was later extended to other six-membered ring derivatives.<sup>2b</sup> Moreover, many authors<sup>4</sup> have excluded the unsubstituted compound in their attempts to realize modified linear free energy *ortho*-correlations.

On the contrary, we have recently shown that in a typical series of five-membered ring *ortho*-like substituted carboxylic acids (3-substituted thiophen-2-carboxylic acids) the acid dissociation constants give a

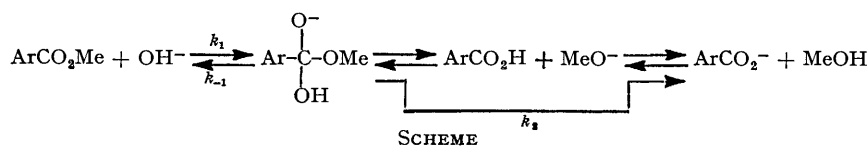


good LFER<sup>5</sup> when the Yukawa-Tsuno treatment<sup>6</sup> as modified by Hoefnagel and Wepster<sup>7</sup> is used. We have also observed LFE *ortho*-correlations in various  $S_NAr$  reactions of thiophen derivatives.<sup>1,8</sup> In every instance<sup>1,5,8</sup> we have included the data related to unsubstituted compounds.

To confirm the general validity of these results we now report kinetic results for the alkaline hydrolysis of methyl esters (I) of some 3-substituted thiophen-2-carboxylic acids (substituents OMe, Me, SMe, H, I, Br, SOMe, and SO<sub>2</sub>Me) in methanol-water (80% v/v) at various temperatures (20–40 °C).

#### RESULTS AND DISCUSSION

**Products and Kinetic Data.**—The alkaline hydrolysis of the methyl esters (I) gives the salts of the corresponding carboxylic acids in high yields, as indicated in the following Scheme. Rate constants and activation parameters are shown in Table I. According to the generally



accepted mechanism ( $B_{AC}2$  in Ingold's classification)<sup>9</sup> with the first step rate-determining and  $k_{obs}$  depending on  $k_1$ , we have observed respectively an increase and a reduction of reactivity on introduction into methyl thiophen-2-carboxylate of an electron-attracting and of an electron-repelling substituent.

**LFERs for the Alkaline Hydrolysis of the Methyl Esters (I).**—In the light of the results obtained for *ortho*-

\* This treatment, although justified from a theoretical viewpoint, is not convenient because it requires a new set of substituent parameters for each *ortho*-, *meta*-, and *para*-like relation of a heterocyclic system.† However, the set of  $\sigma(3-X-2-CO_2H)$  parameters obtained by us represents the first *true* example of *ortho*-like substituent constants of general applicability, directly derived from the Hammett definition of substituent constants.

† This point has been extensively discussed by H. H. Jaffé and H. L. Jones for *meta*- and *para*-like relations in six- and five-membered ring systems (*Adv. Heterocyclic Chem.*, 1964, **3**, 236).

‡ On this point see discussion in ref. 5

§ To calculate  $\rho$  we have used data for the unsubstituted ester and for the esters containing electron-attracting substituents (Table 2, line 2) for which it is reasonable to assume  $\tau^- = 0.00$ .

substituted benzene derivatives, *i.e.* no correlation between logarithms of the rate constants for alkaline hydrolysis of the esters and  $pK_a$  values of the corresponding acids (see above), it was important to search for a LFER between the rate constants for alkaline hydrolysis ( $k_h$ ) of (I) and the dissociation constants of the corresponding acids (II). We have observed an excellent correlation between  $\log k_h$  and  $pK_a$  (Table 2, line 5). If we apply the Hammett proposal, *i.e.*  $\rho + 1.00$ , to the dissociation of the acids (II) in water at 25 °C, the slope calculated (+1.91) represents a  $\rho$  value. It is then possible to define the new set of substituent constants \*  $\sigma(3-X-2-CO_2H) = (-\Delta pK_a)_{X,H}$ , reported in Table 4. When compared to  $\sigma_p^H$ , these constants emphasize a large transmission of substituent effects through the C(2)-C(3) bond of the thiophen ring, as already stated.<sup>1,5,8</sup>

The Hammett plot of  $\log k_h$  versus  $\sigma_p^H$  or versus  $\sigma^n$  gives a poor correlation (see Table 2, lines 1 and 3) with an intercept notably different from zero (respectively  $-0.25$  and  $-0.53$ ). Moreover the value of  $(\log k_h)_{X=SMe}/(\log k_h)_{X=H}$  is  $-0.69$  notwithstanding that the two substituents have much the same  $\sigma_p^H$  and  $\sigma^n$  values.‡

An improvement of statistical results has been obtained by using a Yukawa-Tsuno treatment ( $\rho + 2.77$ ,  $r^+ 0.44$ ,  $R 0.996$ ; see Table 2, line 4) that can weight the 'through-resonance' interactions<sup>7</sup> between electron-repelling substituents and the methoxycarbonyl group.§ This situation is similar to that previously observed by us for the dissociation of the acids (II).

In conclusion, the rate constants for alkaline hydrolysis of the methyl esters (I) show a good LFER with  $pK_a$  values of the corresponding acids. Moreover they satisfy a Yukawa-Tsuno relationship, but give a poor

correlation with  $\sigma_p^H$  or  $\sigma^n$ . These results support the view<sup>1,5,8</sup> that the mode of electronic effect transmission to the reaction centre in five-membered ring *ortho*-like substituted esters is completely different from that for benzene *ortho*-substituted esters (for which LFERs of

<sup>4</sup> M. Charton, *Progr. Phys. Org. Chem.*, 1971, **8**, 235; J. Shorter in 'Advances in Linear Free Energy Relationships,' eds. N. B. Chapman and J. Shorter, Plenum Press, London, 1972, pp. 103–110.

<sup>5</sup> D. Spinelli, R. Noto, and G. Consiglio, *J.C.S. Perkin II*, 1976, 747.

<sup>6</sup> Y. Tsuno, T. Ibata, and Y. Yukawa, *Bull. Chem. Soc. Japan*, 1959, **32**, 960; Y. Yukawa and Y. Tsuno, *ibid.*, 1959, **32**, 965, 971; Y. Yukawa, Y. Tsuno, and M. Sawada, *ibid.*, 1966, **39**, 2274; 1972, **45**, 1198.

<sup>7</sup> A. J. Hoefnagel and B. M. Wepster, *J. Amer. Chem. Soc.*, 1973, **95**, 5357, and previous papers.

<sup>8</sup> D. Spinelli, G. Guanti, and C. Dell'Erba, *J.C.S. Perkin II*, 1972, 441; D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *ibid.*, 1975, 620.

<sup>9</sup> C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell University Press, Ithaca, New York, 2nd edn 1969, p. 1131.

TABLE 1

Rate constants and activation parameters for the alkaline hydrolysis of methyl esters (Ia—h) in methanol–water (80% v/v)

Substituent	$10^3 k/l \text{ mol}^{-1} \text{ s}^{-1} (T/^\circ\text{C})^a$	$\Delta H^\ddagger \text{ kcal mol}^{-1}$	$-\Delta S^\ddagger \text{ cal mol}^{-1} \text{ K}^{-1}$
OMe (Ia)	0.019 9 (20.06), 0.066 7 (30.06), 0.185 (39.99)	19.8	12.4
Me (Ib)	0.050 0 (20.03), 0.142 (30.02), 0.389 (40.12)	18.1	16.4
SMe (Ic)	0.054 4 (20.03), 0.145 (30.02), 0.424 (40.12)	18.0	16.5
H (Id)	0.263 (19.91), 0.709 (30.01), 1.93 (39.99)	17.4	15.2
I (Ie)	0.671 (19.93), 1.67 (30.03), 4.42 (39.95)	16.5	16.5
Br (If)	0.907 (19.91), 2.53 (30.02), 6.38 (39.99)	17.1	13.9
SOMe (Ig)	7.15 (20.10), 20.2 (29.93), 50.4 (40.00)	17.4	8.9
SO <sub>2</sub> Me (Ih)	21.2 (19.97), 48.1 (29.96), 104 (40.12)	13.8	19.0

<sup>a</sup> Rate constants are accurate to  $\pm 3\%$ . <sup>b</sup> At 20 °C the maximum error is 0.5 kcal mol<sup>-1</sup>. <sup>c</sup> At 20 °C the maximum error is 2.0 cal mol<sup>-1</sup> K<sup>-1</sup>.

TABLE 2

Linear free energy relationships <sup>a</sup> for the alkaline hydrolysis of the methyl esters (I) in methanol–water (80% v/v) at 20 °C

Relationship	$\rho \pm \sigma_\rho$	$i \pm s_i$	$R$	Esters
$\log k/k_{\text{H}} = \rho \sigma_{\text{pH}}$	$3.17 \pm 0.26$	$-0.25 \pm 0.09$	0.981	(Ia—h)
$\log k/k_{\text{H}} = \rho \sigma^{\text{n}}$	$2.66 \pm 0.24$	$0.03 \pm 0.12$	0.996	(Ic, g, and h)
$\log k/k_{\text{H}} = \rho \sigma^{\text{n}}$	$3.46 \pm 0.44$	$-0.53 \pm 0.15$	0.955	(Ia—h)
$\log k/k_{\text{H}} = \rho(\sigma^{\text{n}} + 0.44\Delta\sigma_{\text{R}}^+)^{\text{b}}$	$2.77 \pm 0.11$	$0.08 \pm 0.04$	0.996	(Ia—h)
$\log k/k_{\text{H}} = -\rho\Delta pK_{\text{a}}$	$1.91 \pm 0.11$	$0.08 \pm 0.06$	0.991	(Ia—h)

<sup>a</sup>  $\rho$ , reaction constant;  $\sigma_\rho$ , standard deviation of  $\rho$ ;  $i$ , intercept of the regression line with the ordinate  $\sigma$  (or  $-\Delta pK_{\text{a}}$ ) = 0;  $s_i$ , standard deviation of  $i$ ;  $R$ , correlation coefficient; substituents involved in the calculation of  $\rho$  are identified in Table 1; the values of  $\sigma_{\text{pH}}$ ,  $\sigma^{\text{n}}$ ,  $\Delta\sigma_{\text{R}}^+$ , and  $\Delta pK_{\text{a}}$  of the 3-substituted thiophen-2-carboxylic acids used in the correlations are shown in Table 3. <sup>b</sup> The value of  $r^+$  ( $0.44 \pm 0.06$ ,  $R = 0.962$ ) has been calculated by means of the relationship  $(\sigma_{\text{obs}} - \sigma^{\text{n}}) = r^+\Delta\sigma_{\text{R}}^+$ .<sup>7</sup> The values of  $\sigma_{\text{obs}}$  are reported in Table 3.

the same kind are not observed) on account of the differences in geometry between the two kinds of aromatic compound.

## EXPERIMENTAL

*Synthesis and Purification of Compounds.*—Methanol was purified according to the literature method.<sup>10</sup> The acids (II) were converted into the acid chlorides (by the action of thionyl chloride in excess) and then into the esters (I) by treatment with methanol and pyridine. Compounds (Ia, b, and d) were purified by literature methods.<sup>11–13</sup> Physical and analytical data of the esters (Ic and e—h) are in Table 5.

*Kinetic Measurements.*—The method is that used by Chapman, Shorter, and Utley.<sup>14</sup> The rate measurements

TABLE 3

Parameters involved in the calculation of  $\rho$  values

Esters	$\sigma_{\text{pH}}^{\text{a}}$	$\sigma^{\text{n b}}$	$\Delta\sigma_{\text{R}}^{\text{b}}$	$\sigma_{\text{obs}}^{\text{c}}$	$\Delta pK_{\text{a}}^{\text{d}}$	$-\log k_{\text{h}}^{\text{e}}$
(Ia)	-0.268	-0.08	-0.71	-0.43	-0.74	4.695
(Ib)	-0.170	-0.10	-0.22	-0.28	-0.39	4.305
(Ic)	0.00	+0.09	-0.71	-0.27	-0.35	4.276
(Id)	0.00	0.00			0.00	3.582
(Ie)	+0.18	+0.31	-0.18	+0.14	+0.25	3.180
(If)	+0.232	+0.30	-0.16	+0.19	+0.27	3.036
(Ig)	+0.49	+0.49			+0.59	2.145
(Ih)	+0.72	+0.73			+0.95	1.672

<sup>a</sup>  $\sigma$  Values defined by Hammett;<sup>2</sup> for refs. see Table 4. <sup>b</sup> Values from ref. 7. <sup>c</sup> Calculated for the alkaline hydrolysis of esters (I) as in ref. 5. <sup>d</sup>  $\Delta pK_{\text{a}}$  of 3-substituted thiophen-2-carboxylic acids, values from ref. 5. <sup>e</sup> At 20 °C, calculated from activation parameters.

TABLE 4

Substituent	OMe	Me	SMe	H	I	Br	SOMe	SO <sub>2</sub> Me
$\sigma(3\text{-X-2-CO}_2\text{H})$	-0.74	-0.39	-0.35	0.00	+0.25	+0.27	+0.59	+0.95
$\sigma_{\text{pH}}^{\text{a}}$	-0.268	-0.170	0.00 <sup>b</sup>	0.00	+0.18	+0.232	+0.49 <sup>b</sup>	+0.72

<sup>a</sup> From ref. 2a unless noted otherwise. D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.

TABLE 5

Physical and analytical data for the esters (Ic and e—h)

Esters	Cryst. solvent *	M.p. (°C)	Found (%)			Formula	Required (%)		
			C	H	S		C	H	S
(Ic)	LP-PhH	75	44.9	4.5	34.3	C <sub>7</sub> H <sub>8</sub> O <sub>2</sub> S <sub>2</sub>	44.7	4.3	34.0
(Ie) <sup>a</sup>	LP	54	26.8	1.9	12.1	C <sub>6</sub> H <sub>5</sub> IO <sub>2</sub> S	26.9	1.9	11.9
(If) <sup>b</sup>	LP	50	32.9	2.3	14.4	C <sub>6</sub> H <sub>4</sub> BrO <sub>2</sub> S	32.6	2.3	14.5
(Ig)	LP'	112	41.6	3.8	31.4	C <sub>7</sub> H <sub>8</sub> O <sub>3</sub> S <sub>2</sub>	41.2	3.9	31.4
(Ih)	LP-PhH	109	38.5	3.8	29.2	C <sub>7</sub> H <sub>8</sub> O <sub>4</sub> S <sub>2</sub>	38.2	3.6	29.1

<sup>a</sup> Found: I, 47.3; required 47.4%. <sup>b</sup> Found: Br, 36.2; required 36.2%.

\* LP = light petroleum (b.p. 40–60 °C); LP' had b.p. 80–120 °C.

<sup>10</sup> H. Lund and J. Bjerrum, *Ber.*, 1931, **64**, 210.

<sup>11</sup> S. Gronowitz, *Arkiv. Kemi*, 1958, **12**, 239.

<sup>12</sup> W. Steinkopf and W. Hauske, *Annalen*, 1937, **532**, 236.

<sup>13</sup> B. Weinstein, *J. Amer. Chem. Soc.*, 1955, **77**, 6709.

<sup>14</sup> N. B. Chapman, J. Shorter, and J. H. P. Utley, *J. Chem. Soc. (B)*, 1963, 1291.

were carried out by mixing equal volumes of sodium hydroxide (carbonate-free) and ester solutions, both 0.05M, in methanol-water (80% v/v), at the desired temperature and then withdrawing samples at intervals. The samples were quenched in an excess of standard hydrochloric acid

and back-titrated with standard sodium hydroxide solution (Bromophenol Blue).

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