Linear Free Energy *ortho*-Correlations in the Thiophen Series. Part II.[1] Acid Dissociation of Some 3-Substituted Thiophen-2-carboxylic Acids in Water

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The acid dissociation constants of some 3-substituted thiophen-2-carboxylic acids (I; X = OMe, Me, SMe, H, I, Br, SOMe, or SO_2Me) in water, at 25 °, have been measured. The data obtained furnish a good linear free energy relationship of the Yukawa–Tsuno type (ρ +1.34, r^+ 0.57, R 0.996) emphasizing the large difference, probably linked to the geometry of the five-membered ring, from the situation observed for *ortho*-substituted benzoic acids. A $\rho_{2{\cdot}3}/\rho_{2{\cdot}5}$ ratio higher than unity (1.37) has been observed.

RECENTLY the effects of *ortho*-substituents on reaction rates or equilibria have been extensively investigated for benzene systems. Specifically, a large number of acid dissociation constants for *ortho*-substituted benzoic acids [2a] and hydrolysis kinetic constants of the corresponding esters [2b] were collected.

The data obtained have been handled by various approaches, the most significant being those proposed by Taft,[3] Charton,[4] Farthing and Nam,[5] and Chapman

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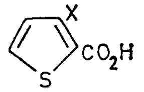
and Shorter.[6] The data * enable the following conclusions to be drawn: (*a*) a linear free energy relationship (l.f.e.r.) can be found only for a limited number of *ortho*-substituents having definite steric and electronic requirements,[11] (*b*) the unsubstituted benzoic acid and the corresponding ester have to be omitted from l.f.e. correlations, (*c*) *ortho*-substituted benzoic acids are stronger than benzoic acid irrespective of the type of substituent, and (*d*) there is no direct correlation between the pK_a of *ortho*-substituted benzoic acids and the kinetic constants of base or acid catalysed hydrolysis of the corresponding esters.[12] Similar results have been obtained for *ortho*-correlations in *e.g.* the naphthalene series,[13] whereas no datum is known for five-membered ring derivatives.

We now report the results of acid dissociation constant measurements of 3-substituted thiophen-2-carboxylic acids (I) (X = OMe, Me, SMe, H, I, Br,



(I)

SOMe, or SO_2Me), for which a different situation can be foreseen. As we have recently pointed out,[1,14a] the geometry of the thiophen ring (and generally of a five-membered ring) causes a reduction of the proximity effects between substituents linked to adjacent positions.

RESULTS AND DISCUSSION

We have measured potentiometrically the acid dissociation constants of some 3-substituted thiophen-2-carboxylic acids in water, at 25° (Table 1). The *ortho*-substituents selected include those recommended by Charton[4] for l.f.e. correlations. A possible deviation from a linear correlation may be evaluated taking into account the unsubstituted acid. The substituents used have large differences in electronic effects, the range covering one unit of $\sigma_p{}^{H}$[15] ($\sigma_{p\text{-OMe}}$ −0.27; $\sigma_{p\text{-SO}_2\text{Me}}$ +0.72).

TABLE 1

pK_a Values of 3-substituted thiophen-2-carboxylic acids in water at 25°

No.	Substituent	pK_a
1	OMe	4.25
2	Me	3.90
3	SMe	3.86
4	H	3.51
5	I	3.26
6	Br	3.24
7	SOMe	2.92
8	SO_2Me	2.56

meta- and para-Like Substituents Effects in Thiophen-2-carboxylic Acids.—The effects of some 4- (*meta*-like) and 5- (*para*-like) substituents on the pK_a in water at 25°, of thiophen-2-carboxylic acid have been measured by Butler[16] and Imoto.[17] There is some discrepancy between these data, which is reflected in the calculated ρ values. For this reason we have measured these acid dissociation constants again and also those of some other substituted acids. The data are collected in Table 2.

TABLE 2

pK_a Values of 4- and 5-substituted thiophen-2-carboxylic acids in water at 25°

No.	Substituent	pK_a [a]	pK_a [b]	pK_a [c]
1	5-OMe	3.78	3.80	3.76
2	5-Me	3.74	3.70	3.76—3.56
3	5-SMe	3.51		
4	H	3.51	3.53	3.49
5	5-I	3.37		
6	5-Br	3.27	3.19	3.30
8	5-SO_2Me	2.81		
9	5-Et	3.65	3.70	
10	5-Cl	3.30		3.41
11	5-NO_2	2.78		2.68
12	4-Me	3.58	3.59	
13	4-Br	3.15		3.11
14	4-NO_2	2.80		2.81—2.86

[a] This work. [b] Values from ref. 16. [c] Values from ref. 17.

The recent re-examination of the Hammett relationship by Wepster and his co-workers[18] has furnished a new set of σ_p values (σ^n) which are independent of the 'through-resonance interactions' between *para*-electron-donating and/or -repelling substituents and the carboxy-group in benzoic acids.

We have utilized this new set of σ values to calculate

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* The peculiar behaviour of *ortho*-substituted benzoic acids in dissociation (solvent water) seems to be linked to specific solvation effects. In fact, the interplanar angle between the phenyl ring and the carboxy-group accounts, in the case of normal substituents ($\eta \leqslant 30°$), for a maximum deviation of 0.1 pK units[7] and the remainder of the deviation depends on the difference in solvation between planar benzoic acid and non-planar *ortho*-substituted benzoic acids as indicated by the results obtained in non-hydroxylic solvents (reaction with 1,3-diphenylguanidine in benzene,[8] dissociation constants in Me_2SO–H_2O,[9] or in concentrated aqueous quaternary ammonium salt solutions[10]). The site of solvation, whether it is the aromatic ring *via* π-electrons or the carboxy-group, is under discussion.

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ρ_m values (Table 3, lines 1 and 2), but the equation $\sigma_{\text{obs}} - \sigma^{\text{n}} = r^+\Delta\sigma_R{}^+$ [18d] gave a discouraging correlation for *para*-substituted benzoic acids as well as for 5-substituted thiophen-2-carboxylic acids (Table 4). Thus, for the treatment of our data we have preferred to make use of the classical Hammett equation.[15a] The ρ values obtained for *meta*- and *para*-substituted benzoic acids and for 4- and 5-substituted thiophen-2-carboxylic acids are virtually identical (Table 3, lines 1 and 3).

TABLE 3

Linear free energy relationships [a] for the dissociation of 3-, 4-, and 5-substituted thiophen-2-carboxylic acids and *ortho*-, *meta*-, and *para*-substituted benzoic acids in water at 25°

Relationship	$\rho \pm s_\rho$	$i \pm s_i$	R	Substituents
$-(\Delta pK_a)_B = \rho\sigma^H$	1.00 ± 0.00	0.00 ± 0.00	1.000	All
$-(\Delta pK_a)_{m,T} = \rho\sigma^n$	0.99 ± 0.04	−0.01 ± 0.01	0.999	4, 12—14
$-(\Delta pK_a)_T = \rho\sigma^H$	0.98 ± 0.02	−0.01 ± 0.01	0.998	1—6, 8—14
$-(\Delta pK_a)_{o,T} = \rho\sigma^H$	1.64 ± 0.15	−0.17 ± 0.05	0.975	1—8
$-(\Delta pK_a)_{o,T} = \rho\sigma^n$	1.29 ± 0.07	−0.01 ± 0.04	0.998	4, 7, 8
$-(\Delta pK_a)_{o.T} = \rho[\sigma^n + 0.57\Delta\sigma_R{}^+]$	1.34 ± 0.05	−0.03 ± 0.02	0.996	1—8
	$\beta \pm s_\beta$			
$-(\Delta pK_a)_{o.T} = -\beta(\Delta pK_a)_{o,B}$	0.70 ± 0.17	−0.47 ± 0.17	0.858	1—8
$-(\Delta pK_a)_{o,T} = -\beta(\Delta pK_a)_{p.T}$	1.64 ± 0.20	−0.14 ± 0.06	0.964	1—6, 8

[a] ρ, reaction constant; β, proportionality constant; s_ρ, standard deviation of ρ; s_β, standard deviation of β; R, correlation coefficient; i, intercept of the regression line with the ordinate σ (or $-\Delta pK_a$) = 0; s_i, standard deviation of i; substituents, actual substituents involved in the calculation of ρ and β, identified according to their number in Tables 1 and 2. The values of σ^H, σ^n, $\Delta\sigma_R{}^+$, and pK_a of benzoic acids used in correlations are shown in Table 5.

TABLE 4

Statistical data [a] for the correlations: $(\sigma_{\text{obs}} - \sigma^n) = r^+\Delta\sigma_R{}^+$

Acid dissociation of	$r^+ \pm s_r$	$i \pm s_i$	R	Substituents
para-Substituted benzoic acids	0.15 ± 0.06	−0.03 ± 0.02	0.701	1—6, 9, 10
5-Substituted thiophen-2-carboxylic acids	0.12 ± 0.08	−0.05 ± 0.03	0.519	1—6, 9, 10
3-Substituted thiophen-2-carboxylic acids	0.57 ± 0.08	−0.01 ± 0.03	0.963	1—6

[a] r^+, Yukawa–Tsuno resonance proportionality constant; s_r, standard deviation of r^+; i, intercept of the regression line with the ordinate $[(\sigma_{\text{obs}} - \sigma^n)] = 0$; s_i, standard deviation of i; R, correlation coefficient. The values of σ_{obs} used in correlations are reported in Table 5, except for *para*-substituted acids for which they coincide with $\sigma_p{}^H$.

TABLE 5

Parameters involved in the calculation of ρ and β values

Substituent	σ^H [a]	σ^n [b]	$\Delta\sigma_R{}^+$ [b]	σ_{obs} [c]	σ_{obs} [d]	$(pK_a)_{o.B}$ [e]
1	−0.268	−0.09	−0.71	−0.26	−0.59	4.09
2	−0.170	−0.10	−0.22	−0.22	−0.29	3.91
3	0.000	+0.09	−0.71	+0.01	−0.26	3.67
4	0.000	0.00	0.00	0.00	0.00	4.20
5	+0.18	+0.31	−0.18	+0.15	+0.20	2.86
6	+0.232	+0.30	−0.16	+0.25	+0.22	2.85
7	+0.49	+0.49				3.10
8	+0.72	+0.73				2.53
9	−0.151	−0.12	−0.19	−0.13		
10	+0.227	+0.29	−0.19	+0.22		
11	+0.778	+0.778				
12	−0.069	−0.069				
13	+0.391	+0.391				
14	+0.710	+0.710				

[a] σ Values defined by Hammett,[15a] from ref. 15*b*. [b] Values from ref. 18*d*. [c] Calculated for the dissociation of 5-substituted thiophen-2-carboxylic acids as in ref. 18*c*. [d] Calculated for the dissociation of 3-substituted thiophen-2-carboxylic acids as in ref. 18*c*, using the ρ value for electron-withdrawing 3-substituents (Table 3, line 5) (see text). [e] Values from ref. 2*a*.

Proximity Effects in Benzene and in Thiophen Derivatives.—To make a comparison between proximity effects in five- and six-membered rings we have plotted the pK_a of 3-substituted thiophen-2-carboxylic acids $[(pK_a)_{o,T}]$ *versus* the corresponding pK_a of *ortho*-substituted benzoic acids $[(pK_a)_{o,B}]$,[2a] but there is no correlation between the two reactions (Figure 1 and Table 3, line 7). We have, therefore, attempted a more reasonable comparison, *i.e.* plotting the pK_a of 3-substituted thiophen-2-carboxylic acids *versus* those of the corresponding 5-substituted thiophen-2-carboxylic acids $[(pK_a)_{p,T}]$ or *versus* $\sigma_p{}^H$ (Figures 2 and 3, and Table 3, lines 8 and 4): in this case a correlation is observed.

The data in Figure 3 display some anomalies. (*a*) Thiophen-2-carboxylic acid and (3-methylthio)thiophen-2-carboxylic acid, *i.e.* two compounds containing substituents with the same $\sigma_p{}^H$ (0.00) show ΔpK_a 0.35 and this makes the intercept calculated different from zero (−0.17); (*b*) the substituents with positive and those with negative σ values produce two different straight lines. To overcome these difficulties we have tried a different correlation for 3-substituted thiophen-2-carboxylic acids, *i.e.* one of the Yukawa–Tsuno (Y–T) type (see Tables 3 and 4).§ This treatment enables a

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§ Since ρ_o is very different from ρ_p and ρ_m (see Table 3), in order to calculate r^+ we have used the ρ value relative to electron withdrawing 3-substituents, supposing for them $r^- = 0.00$.[18c,d]

differentiation between the substituents H and SMe to be made and the special interactions of electron-donating and/or -repelling substituents with the carboxy-group to be estimated. The results are shown in Figure 4. The new treatment of data improves the statistical results and eliminates any doubt about the two different straight lines.

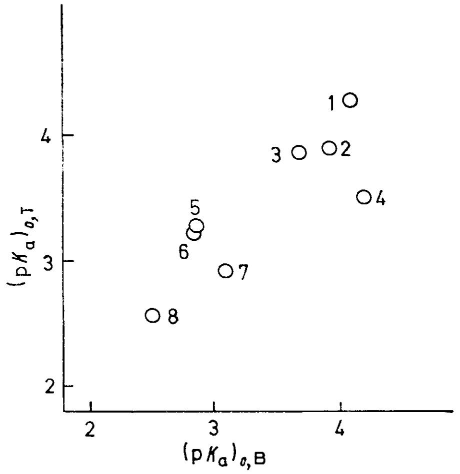

FIGURE 1 Plot of pK_a for 3-substituted thiophen-2-carboxylic acids $(pK_a)_{o,T}$ against pK_a for *ortho*-substituted benzoic acids $(pK_a)_{o,B}$. For substituents see Table 1

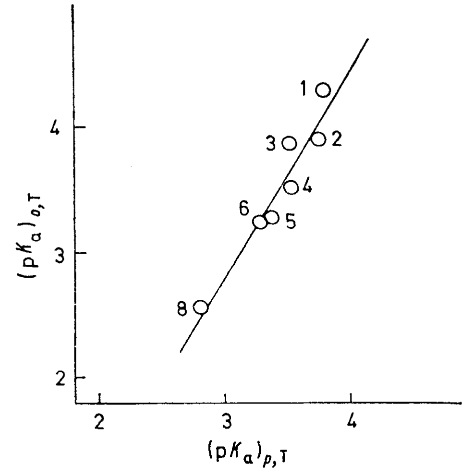

FIGURE 2 Plot of pK_a for 3-substituted thiophen-2-carboxylic acids $(pK_a)_{o,T}$ against pK_a for 5-substituted thiophen-2-carboxylic acids $(pK_a)_{o,B}$

The reason for the difference in behaviour between 3- and 5-substituted thiophen-2-carboxylic acids with respect to the Y–T treatment is connected with the peculiar *ortho*-like relation in a five-membered ring which raises the interactions between the substituents linked to C-2 and -3 of the ring (hyper-*ortho* effect).[19] On the contrary a similar treatment of data for *ortho*-substituted benzoic acids does not improve the correlation.

Comparison of the Influence of Effects of 3- *and* 5-*Substituents*.—This can be made by means of a comparison of the $\rho_{2.5}$ and $\rho_{2.3}$ values. The ratio $\rho_{2.3} : \rho_{2.5}$ obtained (1.37) is higher than unity as expected, confirming the larger transmission [1] of electronic effects between the 2- and 3-positions in the thiophen ring than between the 2- and 5-positions. This fact is strictly linked to the geometry of the five-membered ring which eliminates steric interactions between the two *ortho*-like substituents; moreoever, the high '*bond fixation*' [20] of the thiophen ring produces a high transmission of effects, as supported by the situation observed for *cis*-acrylic acids.[21]

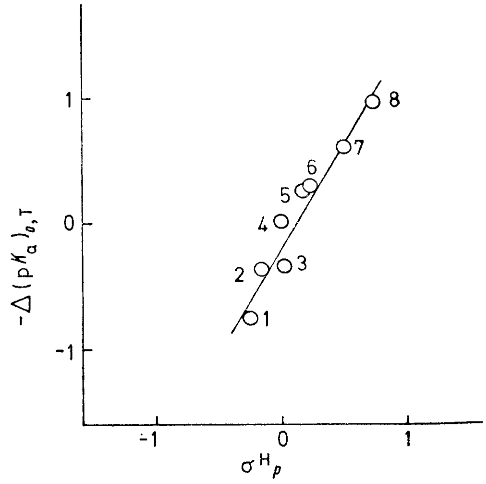

FIGURE 3 Plot of pK_a for 3-substituted thiophen-2-carboxylic acids $(pK_a)_{o,T}$ against $\sigma_p{}^H$

According to our interpretation of the ρ values,[14b] the value of the ratio $\rho_{2,3} : \rho_{2,5}$ indicates that a change in the 3-substituent causes more variation of the position of the transition state for dissociation along the reaction coordinate than does a change in 5-substituent. A similar comparison between *ortho*- and *para*-substituted benzoic acids has no meaning on account of the large difference in solvation between the two series.

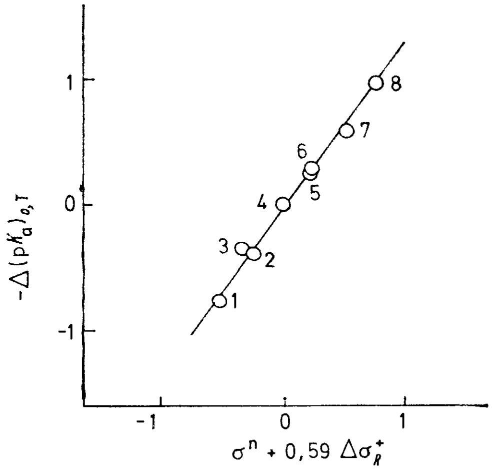

FIGURE 4 Yukawa–Tsuno plot for 3-substituted thiophen-2-carboxylic acids

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Conclusions.—The measurements of pK_a of a series of 3-substituted thiophen-2-carboxylic acids in water at 25° have pointed out a simple l.f.e. correlation for these compounds in contrast to the case of *ortho*-substituted benzoic acids, and show a $\rho_{2.3}:\rho_{2.5}$ ratio higher than unity. The large influence of the geometry of the ring on the possibilities for linear *ortho*-correlations is clearly indicated by the fact that thiophen-2-carboxylic acid does not deviate from the l.f.e.r.

EXPERIMENTAL

Synthesis and Purification of Compounds.—3-Methoxy,[22] 3-methyl-,[23] 3-methylthio-,[24] 3-iodo-,[25] 3-bromo-,[26] 5-methoxy-,[27] 5-methyl-,[28] 5-methylthio-,[29] 5-iodo-,[30] 5-bromo-,[31] 5-methylsulphonyl-,[29] 5-ethyl-,[32] 5-chloro-,[33] 5-nitro-,[34] 4-methyl-,[35] 4-bromo-,[36] 4-nitro-thiophen-2-carboxylic acid,[37] and thiophen-2-carboxylic acid [23] were prepared as reported.

3-*Methylsulphinylthiophen*-2-*carboxylic acid*, m.p. 172° [from light petroleum (b.p. 80—100°)] (Found: C, 37.8; H, 3.2; S, 33.6. $C_6H_6O_3S_2$ requires C, 37.9; H, 3.2; S, 33.7%), and 3-*methylsulphonylthiophen*-2-*carboxylic acid*, m.p. 180° (from aqueous methanol) (Found: C, 35.2; H, 2.8; S, 31.0. $C_6H_6O_4S_2$ requires C, 34.9; H, 2.9; S, 31.1%), were prepared by oxidation[29,38] of (3-methylthio)-thiophen-2-carboxylic acid.

Potentiometric Measurements.—The procedure used for the determination of pK_a values and for calculation of dissociation constants is that described by Albert and Serjeant.[39] The values obtained were reproducible to within ±0.02 pK_a unit. A Radiometer digital PHM 63 pH meter equipped with a Radiometer GK 2301C combined electrode was used for the determinations.

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