(1). Kinetics of Esterification with Diazodiphenylmethane of Some 3-, 4-, and 5-Substituted Thiophene-2-carboxylic Acids in Methanol

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The rate constants for the esterification of some 3-, 4-, and 5-substituted thiophene-2-carboxylic acids with diazodiphenylmethane in methanol at 25° have been measured. The reactivity of some *para*- and *ortho*-substituted benzoic acids has also been determined.

Logarithmic kinetic constants for *ortho*-, *meta*-, and *para*-like substituted thiophene-2-carboxylic acids furnish an excellent linear free energy relationship when plotted *versus* Δpk_a (β 0.89, r 0.989, C.L. > 99.9%, n 18, i 0.04), thus confirming the peculiar behaviour of five-membered ring derivatives. The correlation with σ^H values offers an additional proof of the *hyper-ortho* character of the 2,3-relation in thiophene derivatives. *para*- and *ortho*-Substituted benzoic acids show the usual behaviour of six-membered ring derivatives.

From our studies of the behaviour of various 3-substituted thiophene-2-carboxylic acids (2) (Ia) and of some of their derivatives (Ib,c) [methyl esters (3a) and acyl chlorides (3b)] we have observed good linear free energy (l.f.e.) *ortho*-correlations at variance with the results obtained for six-membered derivatives (5). In particular, acids Ia (2,3) and 2-substituted thiophene-3-carboxylic acids (4) as well as their derivatives give *hyper-ortho* correlations (2), whereas 4-substituted thiophene-3-carboxylic acids show a *hypo-ortho* correlation (1).

In order to extend the scope of l.f.e. *ortho*-correlations involving thiophene derivatives (1-4), we are collecting experimental data concerning the behaviour of *ortho*-like-substituted thiophenecarboxylic acids and their derivatives in various reactions. In this account we report data relative to the reaction of some 3-substituted thiophene-2-carboxylic acids (Ia) with diazodiphenylmethane (DDM) in methanol at 25°.

I

a, Y = OH
b, Y = OMe
c, Y = Cl

Under the same experimental conditions we have also studied the reactivity of various 4- or 5-substituted thiophene-2-carboxylic acids and of some *o*- and *p*-substituted benzoic acids in order to compare the transmission of substituent effects from *para-*, *meta-* and *ortho*-positions in the thiophene and benzene rings.

Results and Discussion.

Products and Kinetic Data.

Carboxylic acids react with DDM giving the corresponding esters (6).

$$R\text{-}CO_2H + Ph_2CN_2 \rightarrow R\text{-}CO_2CHPh_2 + N_2$$
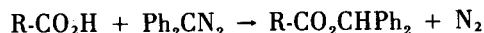
The course of reaction can be followed spectrophotometrically measuring the disappearance of DDM.

In a comparison of reactivity among different series of acids, the reaction between the solvent (methanol) and
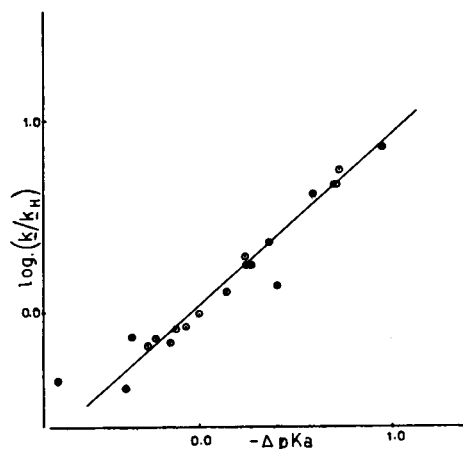

Figure. Logarithmic plot of the kinetic constants for the reaction of some 3-substituted (•) and 4- or 5-substituted (⊙) thiophene-2-carboxylic acids with DDM in methanol at 25° *versus* $-\Delta pK_a$ of the corresponding acids: slope 0.89, r 0.989, n 18. Data for Ia, X = MeO and F have been excluded from the calculation (see text).

Table 1

Rate Constants for Esterification of Carboxylic Acids with Diazodiphenylmethane in Methanol at 25°

10^2 k/l mol^{-1}s^{-1} (a)

No.	Substituent	Benzoic Acids para-Substituted	ortho-Substituted	Thiophene-2-carboxylic Acids 5-Substituted	4-Substituted	3-Substituted
1	NO$_2$	12.2		51.3	43.1	
2	SO$_2$Me		55.4	42.9		67.8
3	SOMe		24.5			38.7
4	Br	4.74	17.8	18.4	21.4	16.5
5	Cl	4.84	16.5			
6	I		17.4	12.0		16.6
7	F		7.19			13.0
8	H	2.66	2.66	9.27	9.27	9.27
9	SMe		5.80			7.11
10	Me	2.09	2.60	6.93	7.96	3.76
11	Et			6.60		
12	i-Pr				7.71	
13	OMe	1.76	3.63	6.34		4.21

(a) Rate constants are accurate to ± 3%.

Table 2

Linear Free Energy Relationships (a) for Esterification of Carboxylic Acids with Diazodiphenylmethane in Methanol at 25°

Relationships	$\varrho \pm s_\varrho$ ($\beta \pm s_\beta$)	$i \pm s_i$	r	n	C.L.
$\log (k/k_H)_B = \varrho\sigma^H$	0.82 ± 0.04	0.04 ± 0.01	0.996	6	99.9
$\log (k/k_H)_{o,B} = \varrho\sigma^H$	1.33 ± 0.15	0.41 ± 0.05	0.961	9 (b)	99.9
$\log (k/k_H)_{o,B} = \beta (-\Delta pK_a)_{o,B}$	0.75 ± 0.10	−0.09 ± 0.11	0.939	9 (b)	99.9
$\log (k/k_H)_{m,p,T} = \varrho\sigma^H$	0.91 ± 0.03	0.01 ± 0.01	0.994	12	99.9
$\log (k/k_H)_{m,p,T} = \beta (-\Delta pK_a)_{m,p,T}$	0.91 ± 0.03	0.03 ± 0.01	0.994	12	99.9
$\log (k/k_H)_{o,T} = \varrho\sigma^H$	1.31 ± 0.09	−0.04 ± 0.03	0.985	9	99.9
$\log (k/k_H)_{o,T} = \beta (-\Delta pK_a)_{o,T}$	0.77 ± 0.10	0.04 ± 0.05	0.946	9	99.9
$\log (k/k_H)_{o,m,p,T} = \beta (-\Delta pK_a)_{o,m,p,T}$	0.81 ± 0.05	0.05 ± 0.02	0.968	20	99.9
$\log (k/k_H)_{o,m,p,T} = \beta (-\Delta pK_a)_{o,m,p,T}$	0.89 ± 0.03	0.04 ± 0.01	0.989	18 (c)	99.9

(a) ϱ and β, susceptibility constants; s_ϱ, standard deviation of ϱ; s_β, standard deviation of β; i, intercept of the regression line with the ordinate σ or $(-\Delta pK_a) = 0$; s_i standard deviation of i; r, correlation coefficient; n, number of points; C.L., confidence level. The values of $(pK_a)_{o,B}$' $(pK_a)_{o,m,p,T}$ and σ^H used in correlations are shown in Table 3. (b) Data for unsubstituted benzoic acid have been excluded from the correlation [cfr., M. Charton, *Prog. Phys. Org. Chem.*, **8**, 235 (1971). J. Shorter, in "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Eds., Plenum Press, London, 1972, pp. 103-110]. (c) Data for 3-fluoro- and 3-methoxythiophene-2-carboxylic acid have been excluded from the correlation.

DDM, which gives the benzhydryl methyl ether, can be neglected (6c). The ratio, R, between the amount of DDM consumed in esterification and the total amount consumed has been measured in some cases and was found to be *ca.* 60%.

In accordance with the generally accepted mechanism (6c), the introduction of an electron-attracting or of an electron-repelling substituent in the *meta-* or *para*-position with respect to the carboxylic group, causes, respectively, an increase or a reduction of reactivity. Similar effects are also observed if the substituents are in the *ortho*-position.

ortho and *para*-Substituted Benzoic Acids.

para-Substituted benzoic acids furnish kinetic data (Table 1) which give an excellent linear free energy relationship (l.f.e.r.) with Hammett sigma values (σ^H) (Table 2, line 1).

Kinetic constants of *ortho*-substituted benzoic acids (Table 1) give l.f.e. *ortho*-correlations with σ^H (Table 2, line 2), but the observed intercept is rather high. The correlation with $-\Delta pk_a$ (Table 2, line 3) is worse, even if the intercept appears more reasonable. These data confirm (6b) that in six-membered derivatives, the proximity effects in the esterification with DDM are quite different from those present in acid dissociation.

The statistical results relative to *ortho*-substituted benzoic acids seem to indicate a substituent effect for the esterification reaction similar to that observed for *para*-substituted benzoic acids. However, at the same time an influence of proximity effects is apparent, which prevents

Table 3

Parameters Involved in the Calculation of ϱ and β values

Substituent	ϱ_p^H (a)	ϱ_m^H (a)	$(pK_a)_{o,B}$ (b)	$(pK_a)_{p,T}$ (c)	$(pK_a)_{m,T}$ (c)	$(pK_a)_{o,T}$ (c)
1	0.778	0.71		2.78	2.80	
2	0.72		2.53	2.81		2.56
3	0.49		3.10			2.92
4	0.232	0.391	2.85	3.27	3.15	3.24
5	0.227		2.92			
6	0.18		2.86	3.37		3.26
7	0.06		3.27			3.11 (d)
8	0.00	0.00	4.20	3.51	3.51	3.51
9	0.00		3.67			3.86
10	−0.17	−0.069	3.91	3.74	3.58	3.90
11	−0.151			3.65		
12		−0.07 (e)		3.62 (d)		
13	−0.268		4.09	3.78		4.25

(a) Values defined by Hammett, from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 240 (1958). (b) Values from references 5a,b. (c) Values from reference 2. (d) D. Spinelli and co-workers, unpublished results. (e) From C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).

a satisfying quantitative correlation with both σ^H and $-\Delta pK_a$.

3-, 4- and 5-Substituted Thiophene-2-carboxylic Acids.

Kinetic data for 4- and 5-substituted acids (Table 1) show excellent linear correlations with both σ^H and $-\Delta pK_a$ (Table 2, lines 4 and 5). The values of susceptibility coefficients indicate substituent effects similar to those observed in the acid dissociation reaction (2).

Kinetic data for 3-substituted thiophene-2-carboxylic acids (Table 1) give a better correlation with σ^H (Table 2, line 6) than with $-\Delta pK_a$ (Table 2, line 7). In accordance with our previous findings (2) the susceptibility coefficient relative to σ^H indicates a high transmission of substituent effects in a 2,3-relation (ϱ 1.31) of five-membered ring derivatives compared to *meta* and *para*-like substituted acids (ϱ 0.91).

According to McLennan (7), it is more correct to use correlations with the $-\Delta pK_a$ values, because in this approach the reference reaction is the dissociation of the corresponding acids. This approach, which is accurate when the substituents are in the *meta*- or *para*-position with respect to the reaction centre, implies that the proximity effects cause similar changes of reactivity in the various reactions of *ortho*-substituted compounds. Nevertheless, if the *ortho*-substituted compounds give globally good linear correlations, a limited number of *ortho*-substituents could give rise to some peculiar interactions which cause them to fall off of the line.

We have obtained a good l.f.e. correlation between kinetic data for reactions of 3-, 4-, and 5-substituted thiophene-2-carboxylic acids with DDM and the $-\Delta pK_a$ of the corresponding acids (Table 2, line 8). An examination of the plot (see Figure) reveals that only two points fail to fall on the line (in Ia, X = F and MeO); excluding them from the calculations improves the statistical data (Table 2, line 9). 3-Methoxy and 3-fluoro-thiophene-2-carboxylic acids react with DDM faster and slower, respectively, than would have been anticipated. This behaviour can be linked to the operation of both "normal" and "reverse" substituent effects (8) (this latter effect being important with small substituents with high charge density) or to hydrogen-bond interactions between the carboxylic acid group and the substituent which can affect the two reactions differently.

Transmission of Substituent Effects of Five-membered Ring Derivatives: Dissociation of Substituted Thiophene-2-carboxylic Acids and Reactivity of Their Derivatives.

The data concerning dissociation of acids, basic hydrolysis of methyl esters, esterification with DDM, and anilinodechlorination of acyl chlorides, when taken together, allow a rough comparison among the transmission of *ortho*-substituent effects in different series of reactions in a side chain of thiophene derivatives. The transmission of substituent effects is quite similar in acid dissociation and in the reaction with DDM in accordance with the similar character of the related transition states which can essentially be depicted as ion pairs (RCO_2^-, HB^+). In basic hydrolysis and in the anilinodechlorination reaction, the substituent effect is larger in accordance with the nature of the reaction intermediate.

As a consequence, on comparing the effect of *ortho*-like substituents in the various reactions *e.g.*, using both σ^H or $-\Delta pK_a$ substituent constants, the basic hydrolysis and the anilinodechlorination give higher susceptibility constants than acid dissociation or esterification with DDM. Moreover, in all the reactions studied the 2,3-relation

behaves as a *hyper-ortho* relation (2), causing higher susceptibility constants with respect to 2,4- (quasi-*meta*) and 2,5- (quasi-*para*) relations.

EXPERIMENTAL

Synthesis and Purification of Compounds.

Methanol (3) was purified as previously reported. Diazodiphenyl-methane (9) was prepared by the method of Smith and Howard; the solutions were stored in a refrigerator. The substituted thiophene-2-carboxylic acids were prepared as previously described (2). The substituted benzoic acids were commercial samples and were purified by crystallization. 2-Methylthio- (5b), 2-methylsulphinyl- (10), 2-methyl-sulphonylbenzoic (10), and 4-isopropylthiophene-2-carboxylic (11) acid were prepared according to literature methods.

Kinetic Measurements.

The rate measurements were performed at 25° (± 0.1°) in the presence of a 10-fold excess ($5 \cdot 10^{-2} M$ in reaction) of the acid, the apparent rate coefficients (k_I) being determined spectrophotometrically. Optical density measurements were made at 525 nm with 1 cm cells and a Beckman DK-2A spectrophotometer. The second-order rate coefficient k_{II} (uncorrected) is given by

$$k_{II} = k_I / \text{acid}$$

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