Linear Free Energy *ortho*-Correlations in the Thiophen Series. Part 7.[1] Kinetics of the Reaction of Some 3-Substituted 2-Thenoyl Chlorides with Aniline in Benzene

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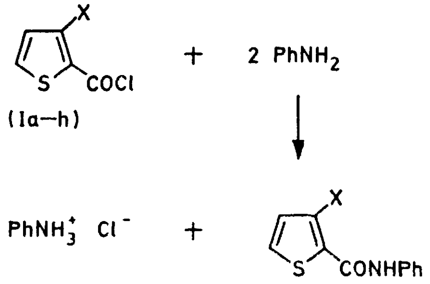
The rate constants for the reactions of some 3-substituted 2-thenoyl chlorides (I; X = OMe, Me, SMe, H, I, Br, SOMe, and SO_2Me) with aniline in benzene have been measured. A plot of the logarithm of the rate constants *versus* the $-\Delta pK_a$ values of the corresponding acids furnishes an example of a non-linear free energy relationship, indicating the occurrence of different reaction mechanisms for 2-thenoyl chlorides with, respectively, electron-attracting and -repelling substituents at C-3.

KINETIC and equilibrium constant measurements have shown that at variance with the results for six-membered systems,[2] five-membered ring compounds give linear free energy (l.f.e.) *ortho*-correlations.[1,3,4] In pursuit of this line of research we now report results for the reactivity of a series of 3-substituted 2-thenoyl chlorides (Ia—h) with aniline in benzene.

The reaction of acid chlorides with anilines has been widely studied both experimentally[5a-d] and theoretically:[5e] it has been regarded as involving attack of the lone pair electrons of the amino group on the carbonyl carbon atom of the acid chloride (rate-determining step). Variations of electronic density on the aniline nitrogen atom and/or on the carbonyl carbon atom induced by the substituent obviously cause large reactivity variations which can give rise to l.f.e. relationships.



SCHEME

The effects of substituents present in aroyl or heteroaroyl halides have been extensively studied: in every case the effects of *meta*- or *para*-substitution have been accounted for by Hammett relationships, which give, for the benzene series, positive susceptibility constants (ρ values usually observed in benzene, +1.4 ± 0.2) according to the proposed mechanism.[5]

RESULTS AND DISCUSSION

Products and Kinetic Data.—3-Substituted 2-thenoyl chlorides (I) react with aniline in benzene to give the corresponding anilides quantitatively (Scheme). The reactions were followed kinetically as previously[5b-d] and in all cases second-order kinetics were observed (*i.e.* first order both in substrate and in aniline). Rate constants and activation parameters are collected in Table 1.

TABLE 1

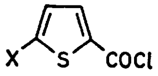
Rate constants and activation parameters for the reaction of 3-substituted 2-thenoyl chlorides with aniline in benzene

Substituent	10^2k/l mol^{-1} s^{-1} (T/°C) [a]	$\Delta H^\ddagger$ [b]/ kcal mol^{-1}	$-\Delta S^\ddagger$ [c]/ cal mol^{-1} K^{-1}
OMe (Ia)	2.62 (15.0), 4.00 (25.0), 7.65 (40.0)	7.1	41.0
Me (Ib) [d]	1.23 (15.0), 1.99 (25.0), 3.82 (40.0)	7.5	41.0
SMe (Ic)	0.782 (15.0), 1.35 (25.0), 2.54 (40.0)	7.8	40.9
H (Id) [e]	1.63 (15.0), 2.52 (25.0), 4.02 (35.0), 6.04 (45.0)	7.4	40.9
I (Ie)	7.88 (15.0), 11.8 (25.0), 21.9 (40.0)	6.7	40.1
Br (If) [d]	9.46 (15.0), 14.3 (25.0), 24.9 (40.0)	6.3	41.1
SOMe (Ig)	8.67 (15.0), 13.2 (25.0), 22.7 (40.0)	6.3	41.4
SO_2Me (Ih)	39.9 (10.0), 53.3 (17.5), 65.5 (25.0)	4.9	42.7

[a] Rate constants are accurate to ±3%. [b] At 20 °C; the maximum error is 0.5 kcal mol^{-1}. [c] At 20 °C. [d] G. Alberghina and S. Fisichella, *J.C.S. Perkin II*, 1978, 81. [e] A. Arcoria, S. Fisichella, G. Scarlata, and D. Sciotto, *J. Org. Chem.*, 1973, **38**, 32.

Linear Free Energy Relationships for the Reactions of Aniline with 3-Substituted 2-Thenoyl Chlorides (I).—Bearing in mind that 3-substituted thiophen-2-carboxylic acids and their derivatives[3b,d] give l.f.e. *ortho*-correlations and, according to the generally accepted mechanism for the reaction of aniline with acid chlorides,[5] one would expect an increase and a reduction of reactivity upon introduction into 2-thenoyl chloride of an electron-attracting and an electron-repelling 3-substituent, respectively. These results have been observed for the 5-substituted 2-thenoyl chlorides (II).[5c]

The calculated activation parameters (see Table 1) show that the reactions studied are isoentropic, with large negative values of the activation entropy in accord with highly polar transition states, and that differences in reactivity are enthalpy-dependent. A break in the trend (increase from $X = SO_2Me$ to $X = SMe$, decrease from $X = SMe$ to $X = OMe$) of the values of the activation enthalpies is observed at $X = SMe$. As a consequence, the kinetic data furnish a pattern which is apparently contradictory in that the introduction into 2-thenoyl chloride of an electron-attracting 3-substituent causes an increase of reactivity; the methylthio * and methyl groups produce a small decrease of reactivity, and the methoxy group causes an increase of reactivity.


(II)

Previously it has been pointed out that the reactions with aniline, respectively, of 3-bromo- and 3-methyl-2-thenoyl chlorides and of 5-substituted 2-thenoyl chlorides (II) obey a unique l.f.e.r.[5d] Therefore we have plotted the logarithms of the rate constants for anilino-substitution of chlorides (I) and (II) *versus* the pK_a or better the $-\Delta pK_a$ values † (see Table 2) of the corresponding acids in water at 25 °C (see Figure) and we have observed a unique l.f.e.r. for chlorides (Ic—h) and (II) with a positive susceptibility constant.

TABLE 2

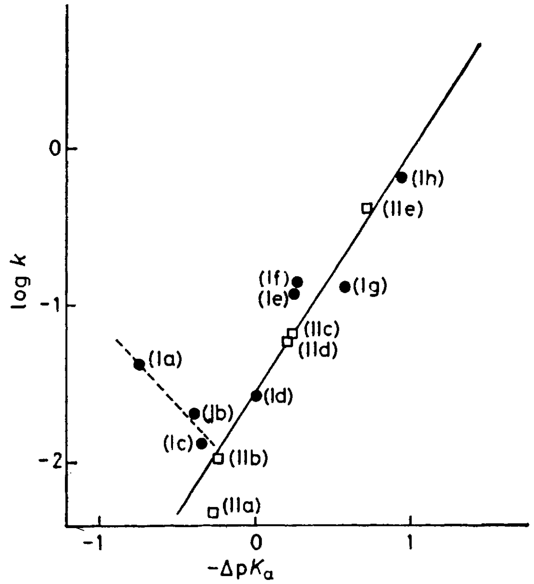
Calculated [a] log *k* at 25 °C for the reaction of substituted 2-thenoyl chlorides with aniline and $-\Delta pK_a$ of the corresponding acids [b]

Substituent	log *k*	$-\Delta pK_a$
3-OMe (Ia)	−1.390	−0.74
3-Me (Ib)	−1.703	−0.39
3-SMe (Ic)	−1.884	−0.35
H (Id)	−1.589	0.00
3-I (Ie)	−0.921	+0.25
3-Br (If)	−0.847	+0.27
3-SOMe (Ig)	−0.884	+0.59
3-SO_2Me (Ih)	−0.179	+0.95
5-OMe (IIa)	−2.328	−0.27
5-Me (IIb)	−1.982	−0.23
5-Br (IIc)	−1.190	+0.24
5-Cl (IId)	−1.229	+0.21
5-NO_2 (IIe)	−0.376	+0.73

[a] From activation parameters: see Table 1 and G. Alberghina, A. Arcoria, S. Fisichella, and G. Scarlata, *Gazzetta*, 1973, **103**, 319. [b] D. Spinelli, R. Noto, and G. Consiglio, *J.C.S. Perkin II*, 1976, 747 and references therein.

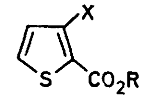
On the other hand, the points for chlorides (Ia—c) show a different reactivity trend (negative susceptibility). Thus chlorides (Ia—h) as a whole furnish an example of a non-linear concave upward free energy curve: this kind of relationship is usually considered as a proof for a changeover of mechanism as a function of the substituent present.[6]

On the basis of our data we suggest that whereas chlorides (Ic—h) (*ortho*-like isomers) as well as the *para*-like isomers (II) react through the generally accepted mechanism, chlorides containing strongly electron-repelling substituents react by a different mechanism,‡ compound (Ic) being the break point. As for the possibility of including all the substituents in a unique *linear* free energy correlation we do not consider the two straight lines in the Figure to be a mere consequence of the scatter (see Experimental section).



Logarithmic plot of the kinetic constants for the reaction of some 3-substituted (Ia—h) and 5-substituted (IIa—e) 2-thenoyl chlorides with aniline in benzene at 25 °C *versus* $-\Delta pK_a$ of the corresponding acids: slope 1.54, *r* 0.956, *n* 11. Data for (Ia and b) have been excluded from the calculation (for explanation of the dotted line, see text)

The l.f.e.r. now observed conforms to previous results on the dissociation constants [3b] of acids (III) and the alkaline hydrolysis [3d] of methyl esters (IV).


(III) R = H
(IV) R = Me

Moreover the correlation slope calculated for thenoyl chlorides (Ic—h) and (II) can be treated as a true ρ value bearing in mind that, as we have already pointed

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* Thiophen-2-carboxylic acid in water at 25 °C is stronger than its 3-methylthio derivative (ΔpK_a − 0.35),[3b] indicating that in the series of 3-substituted thiophen-2-carboxylic acids the methylthio group behaves as an electron-repelling substituent.

† As we have already pointed out [3d] the $-\Delta pK_a$ values used represent a true set of substituent constants [σ(3–X–2–CO_2H)].

‡ Many other examples of curved Hammett plots concerning nucleophilic substitutions at an sp^2 hybridized carbon atom are known. Classical examples are the hydrolysis of acyl halides,[7] carboxylic acid anhydrides,[8] and *C*-chloroazomethine systems.[9] In each case the experimental data have been interpreted on the basis of the intervention of two different reaction mechanisms. A reaction, which seems similar to the anilinodechlorination studied by us, is the aminodechlorination of some diarylimidoyl chlorides in benzene studied by Ta-Shma and Rappoport.[9d] They rationalize the data obtained on the grounds of a normal nucleophilic addition mechanism for electron-attracting substituents and of a dissociative [presumably $S_N2(IP)$] mechanism for electron-donating substituents. In our case a similar situation can be assumed, bearing in mind that the 2,3-relation in five-membered ring derivatives, because of its hyper-*ortho* character, can strengthen the opportunity for a dissociative mechanism by through-resonance or by a field effect.

TABLE 3

Physical and analytical data for 3-substituted thiophen-2-carbanilides [a] and 2-thenoyl chlorides

		Found (%)			Carbanilide	Required (%)			Chlorides B.p. (°C)
Substituent	M.p. (°C)	C	H	N	Formula	C	H	N	(*p*/mmHg)
OMe	85	61.7	4.8	6.1	$C_{12}H_{11}NO_2S$	61.8	4.8	6.0	110/4
SMe	86	57.9	4.4	5.6	$C_{12}H_{11}NOS_2$	57.8	4.4	5.6	143/0.4
I	106	40.0	2.4	4.2	$C_{11}H_8INOS$	40.1	2.4	4.3	96/1 [b]
SOMe	122	54.3	4.1	5.2	$C_{12}H_{11}NO_2S_2$	54.3	4.2	5.3	151/0.4 [c]
SO_2Me	164	51.3	3.9	4.8	$C_{12}H_{11}NO_3S_2$	51.2	3.9	5.0	160/0.3

[a] Crystallized from aqueous ethanol. [b] M.p. 96°, from ligroin. [c] M.p. 68°, from ligroin.

out, the $-\Delta pK_a$ values can be considered as true $\sigma(\text{3-S-2-CO}_2\text{H})$ values.[3d] The slope obtained is of the same order of magnitude as those observed in the case of benzoyl chlorides: therefore, taking into account the fact that the $|\sigma(\text{3-X-2-CO}_2\text{H})|$ values are higher than the corresponding benzene $|\sigma_p|$ values we can say that the present results confirm the previous statement that the 2,3-relation in thiophen compounds is a hyper-*ortho* relation characterized by a high transmission of electronic effects. On the other hand the possibility of a l.f.e.r. agrees with the previous observations that in five-membered ring derivatives the presence of a 3-substituent (*ortho*-like) does not much affect the reactivity of a side-chain in the 2-position by steric interactions [3b,d] because of the peculiar geometry of these rings.[10]

EXPERIMENTAL

Synthesis and Purification of Compounds.—The 3-substituted 2-thenoyl chlorides and the 3-substituted thiophen-2-carbanilides were prepared by well known procedures.[5b-d]

Physical and analytical data are collected in Table 3.

Aniline was purified by repeated distillation at reduced pressure. Benzene (R. P. Carlo Erba) was used as solvent without further purification.

Kinetic Measurements.—The reactions were followed kinetically, as previously reported.[5b-d] The initial concentrations of the reactants after mixing were thenoyl chloride 0.005M and aniline 0.01M.

Calculations.—The correlation of logarithmic kinetic constants (log k_{25°) with $-\Delta pK_a$ values (all substituents included) is statistically significant at better than the 0.1% level.

Nevertheless, inspection of the Figure shows that the 3-methoxy-substituted derivative markedly deviates from the straight line defined by the other substituents: moreover the calculated intercept is much different from the experimental value. Because of the activation enthalpy values (see text) we suggest that the 3-methoxy- as well as the 3-methyl-substituted compound should be excluded from the correlation. In this case a reaction mechanism peculiar to electron-repelling and/or -donating substituents probably operates and we feel that our choice of the correlation line is well founded.

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