The Dependence of the ρ Values of Electrophilic Substitutions upon the Nature of the Aromatic Substrate: Trifluoroacetylation of Substituted Furans, Thiophens, and Pyrroles [1,2]

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ρ Constants for electrophilic substitutions vary with the nature of the aromatic reference substrate, as shown by an examination of the data available in the literature and by a comparative study of substituent effects in the trifluoroacetylation of furan, thiophen, and pyrrole nuclei. The differences in sensitivities to structural changes are discussed in term of different positions of the transition states along the reaction co-ordinates.

ELECTROPHILIC substitutions of monosubstituted benzenes exhibit a wide range of ρ values [3] which reflect different degrees of sensitivity to structural changes.

Currently [4-6] it is believed that the magnitude of the ρ value reflects the nature of the transition state of the reaction. Reactions with powerful electrophiles have 'early' transition states (of the oriented π-complex type) and correspondingly small, negative ρ values, in contrast with reactions involving very mild electrophiles which have transition states close to the Wheland intermediate and show a wide range of reactivity with different substrates. Shatenshtein [7] has compared this behaviour to the well known levelling effect of strong acids in acid-base reactions.

The variation of ρ values for the same electrophile and different substrate series has received less attention.

The few data available for benzene derivatives seem to indicate that the substitutions for more nucleophilic systems are less 'selective'. Thus, the ρ constants for the halogenation of substituted polymethylbenzenes and anisoles are small compared with those for chlorination and bromination of monosubstituted benzenes (Table 1). However, the differences in ρ values could arise either from the different nucleophilicity of the reference compound or the different steric environment at the reaction centre.[8]

TABLE 1

ρ Values for halogenation reactions

Substrates	ρ Chlorination	ρ Bromination	Ref.
Monosubstituted benzenes	−10·0	−12·1	*a*
Substituted polymethylbenzenes	−7·5	−8·9	*b*
para-Substituted anisoles [d]	−7·2	−8·7	*c*

[a] L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, 1963, **1**, 35. [b] E. Baciocchi and G. Illuminati, *Progr. Phys. Org. Chem.*, 1967, **5**, 1. [c] The ρ value for chlorination has been calculated utilizing data of the literature (A. E. Bradfield and B. Jones, *J. Chem. Soc.*, 1928, 1006; A. E. Bradfield, W. O. Jones, and F. Spencier, *J. Chem. Soc.*, 1931, 2913; B. Jones, *J. Chem. Soc.*, 1938, 1414; B. Jones and E. N. Richardson, *J. Chem. Soc.*, 1956, 3939). The ρ value for bromination is derived from unpublished data of H. C. Brown, G. Marino, and R. Wirkkala. [d] Reactivities of 2-position (*meta* to the substituent).

More interesting is the comparison for quite different aromatic systems, *e.g.* thiophens. In dealing with the reactivities of substituted thiophens, it is customary to compare the pairs of positions 2,5 (of 'conjugative' type) and 2,4 ('non-conjugative') of thiophen to the pairs of positions 1,4 (*para*) and 1,3 (*meta*) of benzene. Accordingly, the conventional $\sigma_p{}^+$- and $\sigma_m{}^+$-constants (derived for benzenes) are employed to calculate the ρ constants for the reactions at the thiophen ring.

In Table 2, the ρ values available in the literature for substitutions at the thiophen ring are compared with the ρ values of the corresponding reactions of benzene derivatives.

TABLE 2

A summary of the ρ values for electrophilic substitutions of substituted benzenes and thiophens

Reaction	ρ, Benzenes [a]	ρ, Thiophens	Ref.
Bromination	−12·1	−10·0	*b*
Chlorination	−10·0	−7·8	*c*
Protodetritiation	−8·2	−7·2	*d*
Acetylation	−9·1	−5·7	*e*
Mercuration	−4·0	−5·3	*f*

[a] L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, 1963, **1**, 35. [b] G. Marino, *Atti Accad. naz. Lincei. Rend. Classe Sci. fis. mat. nat.*, 1965, **38**, 700. [c] The ρ value for chlorination of substituted thiophens has been calculated using the data of A. R. Butler and J. B. Hendry, *J. Chem. Soc.*, 1970, 848 and additional unpublished data of G. Marino. [d] A. R. Butler and C. Eaborn, *J. Chem. Soc.* (*B*), 1968, 370. [e] Data from ref. 26 and S. Clementi, P. Linda, and M. Vergoni, *Tetrahedron*, 1971, **27**, 4667. [f] Data from R. Motoyama, J. Ogawa, and E. Imoto, *Nippon Kagaku Zasshi*, 1957, **78**, 962.

In all the reactions examined † except one, the ρ values for the thiophen reactions are always smaller than those for the benzene reactions. The only exception is that

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† It must be noted, for precision, that the conditions for acetylation and protodetritiation were not the same for the thiophen and the benzene derivatives.

[1] This paper is considered as Part XIV of the series, Electrophilic Substitutions in Five-membered Heteroaromatic Rings, Part XIII, P. Linda, G. Marino, and S. Santini, *Tetrahedron Letters*, 1970, 4223.

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for mercuration, and here there is good reason to believe that the reaction occurs by a different mechanism.[9,10]

In order to clarify the correlation between the nature of the aromatic ring and its sensitivity to substituent effects in electrophilic substitution additional information is necessary. The data reported in this paper, together with that previously published,[11] allow us to compare the reactivities of the furan, thiophen, and pyrrole nuclei to trifluoroacetylation.

RESULTS AND DISCUSSION

The rates of trifluoroacetylation relative to the parent heterocycles of 18 α-substituted derivatives of furan, thiophen, and pyrrole have been determined by a competitive procedure (Table 3). In each case a single substitution product was obtained, to which the structure of the αα′-disubstituted derivative has been assigned. The data of Table 3 can therefore be discussed as referring to α-reactivities.

TABLE 3

Relative rates of trifluoroacetylation of 2-substituted furans, thiophens, and pyrroles in dichloroethane, at 75°

	k/k_0 [a]		
Substituent	Furans	Thiophens	Pyrroles
OMe		$1{\cdot}8 \times 10^{6}$ [b]	
SMe	$1{\cdot}7 \times 10^{4}$	$5{\cdot}2 \times 10^{3}$ [b]	
Me	$1{\cdot}7 \times 10^{3}$ [b]	$3{\cdot}8 \times 10^{2}$ [b]	23·8
Et	$1{\cdot}4 \times 10^{3}$	$5{\cdot}2 \times 10^{2}$	24·8
Bu^t	$8{\cdot}6 \times 10^{2}$	$5{\cdot}4 \times 10^{2}$	24·8
Ph	$3{\cdot}0 \times 10^{2}$	$1{\cdot}1 \times 10^{2}$	
H	1	1	1
Cl	$7{\cdot}1 \times 10^{-2}$	$5{\cdot}8 \times 10^{-1}$	
Br	$3{\cdot}6 \times 10^{-2}$	$4{\cdot}6 \times 10^{-1}$	

[a] Relative rates of substitution at the 5-position. The values are corrected for the statistical factor. [b] Calculated from data of ref. 11.

Plots of log k/k_H for thiophen and furan derivatives against σ_p^+-constants are linear and yield ρ values of −7·4 and −10·7, respectively.*

Only one major deviation from linearity occurs in the plots, that for the methylthio-group; it has been noted, however that this also occurs for $\rho\sigma^+$ plots for benzene substitutions and the reason has been discussed in a recent paper.[12]

Unfortunately the available data for pyrroles are limited to the alkyl derivatives and, therefore, do not permit the testing of the applicability of a linear free-energy relationship. Nevertheless, they do show that the sensitivity of the pyrrole ring to substituent effects is less than that of the other two rings.

This behaviour favours the hypothesis that the transition state for substitutions at the very reactive pyrrole ring will occur at a point along the reaction co-ordinate far removed from the Wheland intermediate; it will, therefore, have more π-character.

In contrast, in furan the rate of substitution is more greatly influenced by structural changes: this is taken to indicate that the transition state here resembles the σ-complex. The behaviour of thiophen is intermediate between those of the other two systems.

Although small, the differences in the reactivities of the various alkyl derivatives are thought to be significant. The order of reactivity observed seems to confirm the above mentioned hypothesis. In fact, the reactivities of the alkylfurans follow the order of the hyperconjugative effect (Me > Bu^t), which is of importance in the stabilization of the intermediate. In contrast, the reactivities of the alkylpyrroles (and the alkylthiophens) follow the inductive order (Bu^t > Me) which is believed to be mainly responsible for the electronic distribution in the ground states of the alkyl derivatives [see, for instance, the values of the dipole moments [13] of toluene (0·30 D) and t-butylbenzene (0·70 D)].

It may be interesting to note that the observed order of ' substrate selectivity ' in the trifluoroacetylation, parallels the order of ' positional selectivity ': in all the electrophilic substitutions for which data are available for a comparison, the α : β reactivity ratio decreases in the order : furan > thiophen > pyrrole.[14]

However, further data on other electrophilic substitutions of these rings are desirable, before any conclusions of a general nature are drawn.

EXPERIMENTAL

Starting Materials.—Thiophen (b.p. 84°), 2-methylthiophen (112·5°), 2-ethylthiophen (133°), 2-chlorothiophen (124°), 2-bromothiophen (150°), and pyrrole (131°) were pure grade commercial samples, purified by distillation at atmospheric press.

2-Methylpyrrole [15] (148°) and 2-methylthiothiophen [11] (73°/20 mm) were available from previous studies.

2-t-Butylthiophen [16] (b.p. 165°), 2-phenylthiophen [17] (m.p. 33°), 2-bromofuran [18] (b.p. 100°), 2-ethylfuran [19] (92°), 2-t-butylfuran [20] (115°), 2-methylthiofuran [21] (65°/20 mm), 2-phenylfuran [22] (96°/10 mm), 2-ethylpyrrole [23] (160°), and 2-t-butylpyrrole [24] (m.p. 45°) were prepared by literature methods.

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* Correlations with the exclusion of the *p*-methylthio-group.

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2-Chlorofuran was prepared by treating furan (50 ml, 0·7 mol) in chlorobenzene (100 ml), cooled in an ice-bath, with SO_2Cl_2 (30 ml., 0·35 mole) in the solvent (50 ml). The excess of substrate is necessary to prevent disubstitution; the reagent was added very slowly. The mixture was set aside overnight and then poured into crushed ice and extracted by ether. The organic layer was neutralized, dried (Na_2SO_4), and distilled. The fraction, b.p. 70—90°, when redistilled, gave 6·1 g (16%) of pure product (b.p. 76°; lit.[25]: 77°).

Trifluoroacetic anhydride was a commercial product (Fluka) distilled over P_2O_5, b.p. 39°. 1,2-Dichloroethane (Erba) was dried over P_2O_5 and distilled through a Todd column; the medium fraction b.p. 83—83·5°, was used.

Trifluoroacetyl Derivatives.—2-Trifluoroacetylthiophen, 2-methyl-5-trifluoroacetylthiophen, 2-trifluoroacetylpyrrole, 2-methyl-5-trifluoroacetylpyrrole, and 2-methylthio-5-trifluoroacetylthiophen were available from previous studies.[11,15]

The trifluoroacetyl derivatives of the other substrates are new compounds and were prepared by reaction of the aromatic compound with trifluoroacetic anhydride in dichloroethane. The mixtures were poured into aqueous sodium hydrogen carbonate and the organic layer was separated and dried; solvent was distilled off. The residues were distilled at reduced pressure, or sublimed.

In some typical cases (reactions of 2-methylthiophen,[11] 2-methylfuran,[11] 2-methylpyrrole,[15] 2-methoxythiophen,[11] 2-methylthiothiophen,[11] 2-ethylfuran, 2-ethylpyrrole, 2-chlorothiophen, and 2-bromothiophen), the isomer formed was identified without ambiguity as the 5-trifluoroacetyl-2-substituted derivative by the examination of the n.m.r. spectrum. There is no reason to suppose that the other compounds behave differently; accordingly, the structure of 5-trifluoroacetyl derivative was assigned to the products formed in all the cases. Table 4 summarizes reaction conditions, physical properties, and analytical data for all the trifluoroacetyl derivatives not previously described.

TABLE 4

5-Trifluoroacetyl-2-R-substituted thiophens, furans, and pyrroles

	R	Reaction conditions	M.p. or b.p./20 mm	Found (%)			Required (%)		
				C	H	N	C	H	N
Thiophens	Et	5 days at 75°	85° (b)	46·15	3·4		46·0	3·55	
	Bu^t	5 days at 75°	110° (b)	50·85	4·7		50·6	4·85	
	Ph	5 days at 110°	87° (m)	56·25	2·75		56·25	2·8	
	Cl	15 days at 130°	75° (b)	33·6	0·95		33·4	0·95	
	Br	15 days at 130°	84° (b)	27·8	0·8		28·05	0·75	
Furans	Et	30 min at 25°	76° (b)	50·0	3·65		50·2	3·65	
	Bu^t	30 min at 25°	96° (b)	54·55	5·05		54·5	5·1	
	Ph	30 min at 25°	66° (m)	60·0	2·95		60·1	2·95	
	Cl	30 days at 75°	145° (b/atm)	35·3	1·0		36·3	1·0	
	Br	30 days at 75°	73° (b)	29·65	0·85		29·9	0·85	
	SMe	30 min at 25°	30° (m)	40·0	2·4		39·8	2·45	
Pyrroles	Et	5 min at 25°	62° (m)	50·25	4·2	7·35	49·8	4·05	7·35
	Bu^t	5 min at 25°	104° (m)	54·8	5·5	6·4	54·55	5·65	6·4

Competitive Experiments.—The competitive experiments were carried out at 75° by using the procedure described in previous papers.[11,26] The average values for the relative rates for each pair of substrates examined are reported in Table 5.

TABLE 5

Competitive experiments of trifluoroacetylation

Compound (I)	Compound (II)	No of experiments	k_I/k_{II}
Thiophen	2-Chlorothiophen	3	3·48
Thiophen	2-Bromothiophen	3	4·35
2-Phenylthiophen	Thiophen	3	55·2
2-Ethylthiophen	2-Methylthiophen	3	1·40
2-t-Butylthiophen	2-Methylthiophen	3	1·42
2-Chlorofuran	Thiophen	3	4·96
2-Bromofuran	Thiophen	3	2·53
2-Phenylfuran	2-Methylthiothiophen	3	8·15
2-Ethylfuran	2-Methylthiothiophen	2	37·3
2-Ethylfuran	2-t-Butylfuran	2	1·62
Pyrrole	2-Thiomethoxyfuran	2	44·4
2-Methylpyrrole	Pyrrole	3	11·9
2-Ethylpyrrole	Pyrrole	3	12·4
2-t-Butylpyrrole	Pyrrole	3	12·4

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