Substituent Effects in Homolytic Substitution Reactions: Phenylation of Some 2-Substituted Thiophens

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Homolytic substitution of 2-substituted thiophens with phenyl radicals occurs predominantly at the 3- and 5-positions; the ratio of isomers is dependent on the electronegativity of the 2-substituent. Total and partial rate factors for the phenylation reaction relative to the rate of phenylation of thiophen have been determined: halogen substituents deactivate and methyl, methoxycarbonyl and nitro-substituents activate the thiophen ring towards substitution.

THE effect of substituents on homolytic aromatic substitution has been thoroughly investigated only for mono-[1] and di-substituted[2] benzenes.

Continuing our studies on the homolytic reactivity of thiophen,[3] we have tried to ascertain the effect of 2-substituents on the reactivity of the other positions with respect to homolytic phenylation. Thus, phenyl radicals have been generated in equimolecular mixtures of thiophen and 2-X-substituted thiophen, and the reaction mixtures have been examined to determine the quantities of 2- and 3-phenylthiophen and 3-, 4-, and 5-phenyl-2-X-thiophens formed.

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[2] D. I. Davies, D. H. Hey, and B. Summers, *J. Chem. Soc.* (*C*), 1970, 2653; 1971, 2681.

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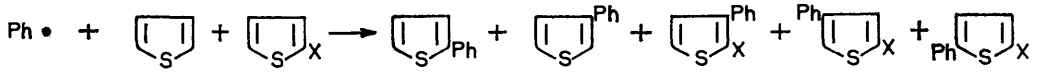


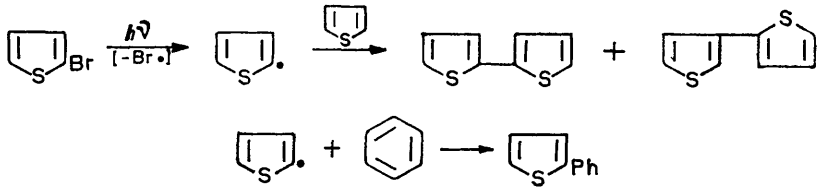
(I) (II) (III) (IV) (V)

(X = Me, Br, Cl, CO_2Me, NO_2)

$$k_3 = 2\frac{\text{mole (III)}}{\text{mole (I)}};\quad k_4 = 2\frac{\text{mole (IV)}}{\text{mole (I)}};\quad k_5 = 2\frac{\text{mole (V)}}{\text{mole (I)}}$$

The ratios k_3, k_4, and k_5 represent the reactivity of the 3-, 4-, and 5-positions of the substituted thiophen relative to the 2-position of thiophen under prescribed conditions.[1] Similarly $k'_3 = 2\frac{\text{mole (III)}}{\text{mole (II)}}$ represents the reactivity of the 3-position of the substituted thiophen relative to the 3-position of thiophen.

Phenyl radicals were generated by decomposition of *N*-nitrosoacetanilide [1] and by aprotic diazotization of aniline.[4] The photolysis of iodobenzene [1] gave good results only in the phenylation of 2-methylthiophen; no bithienyls were formed and no isomerization of the phenylthiophens [5] occurred. The other substrates were insufficiently transparent to u.v. light to allow the photolysis of iodobenzene; irradiation of a solution of bromothiophen in thiophen gave bithienyls, *via* fission of the thienyl–Br bond and homolytic substitution by the thienyl radical formed.



Similarly, phenylthiophen was formed during irradiation of a solution of bromothiophen in benzene. No fission of the C–Br bond of bromobenzene was observed under similar conditions.

The anomalous behaviour of benzoyl peroxide in the presence of thiophen [6] precluded its use as a phenyl radical source in these reactions.

Quantitative determination by g.l.c. of the phenylthiophens present was made on the crude reaction mixtures, in order to avoid selective removal of the low-boiling isomers during work-up. Only phenylation products were detected except in the phenylation reaction of 2-methylthiophen, in which some 2,2′-dithienylethane, derived from the dimerization of the 2-thienylmethyl radical formed by hydrogen abstraction, was also obtained.

The yields of phenylation products (40—70%) were higher when *N*-nitrosoacetanilide was used, but the relative reactivities and the isomer ratios were the same within the limits of experimental error with both the radical sources; again, the relative reactivities and the isomer ratios were unchanged when the reactions were carried out with non-equimolecular proportions of the two substrates and the results were adjusted for their relative concentrations; finally, the isomer ratios obtained in the phenylation of the substituted thiophens alone coincide within the limits of experimental error with those obtained in the competitive experiments.

From these experimental features, it is reasonable to conclude that the data obtained are reliable partial rate factors for the phenylation reaction.

The isomer ratios obtained in the phenylation experiments are reported in Table 1.

The high selectivity of thiophen towards phenylation is lost on introduction of a 2-substituent; thus the α : β ratio of 13 : 1 for the unsubstituted parent compound contrasts with the 1 : 1 ratio for 2-methoxycarbonylthiophen: The *meta*-like 4-position is little affected by the presence of a substituent.

These results can be qualitatively explained in terms of the resonance structures of the α-complexes for attack of the phenyl radical on the thiophen nucleus.

TABLE 1

Isomer ratios in the phenylation of 2-X-thiophen

	% 3 (or β)		% 4		% 5 (or α)		
X	(A)	(B)	(A)	(B)	(A)	(B)	5/3
H(*)	7				93		
Me	16·6	16·6	4·0	4·4	79·4	79·0	4·8
Br	30·1	31·7	4·6	3·6	65·3	64·7	2·1
Cl	34·3	33·7	5·9	7·3	59·8	59·0	1·75
CO_2Me	49·7	49·7	2·0	2·0	48·3	48·3	0·97
NO_2	77·0	76·8			23·0	23·2	0·30

Phenylating agent: (A) = *N*-nitrosoacetanilide; (B) = aprotic diazotization of aniline. The phenylation of 2-methylthiophen by photolysis of iodobenzene gave: 3% = 16·0; 4% = 4·6; 5% = 79·4.

* Ref. 3.

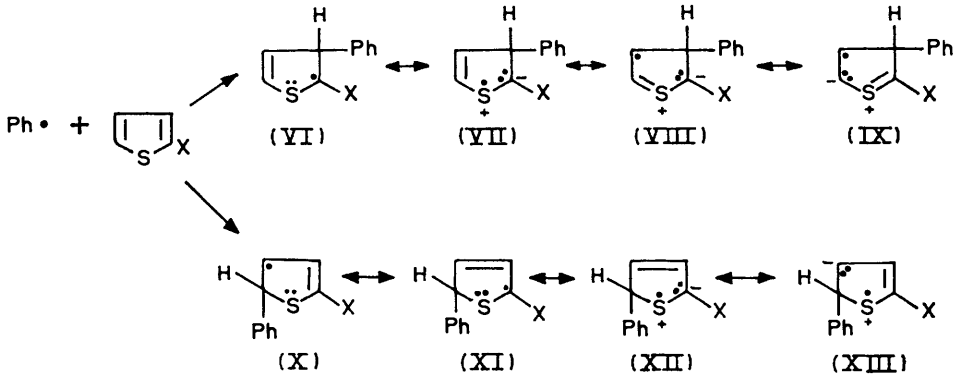
For the unsubstituted compound, the large energy differences between the forms (VI), (X), and (XI) and of the ' polar ' forms (VII), (VIII), (IX), (XII), and (XIII) can

[4] J. I. G. Cadogan, *J. Chem. Soc.*, 1962, 4257.

[5] H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beekhuis, *J. Amer. Chem. Soc.*, 1956, **89**, 3501.

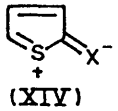
[6] C. E. Griffin and K. R. Martin, *Chem. Comm.*, 1965, 154; a detailed analysis of this reaction is now under examination in our laboratories.

explain the preference for the attack in the α-position. Introduction of a substituent stabilizes the dipolar forms and the energy difference between the two σ-complexes is destroyed; attack at the 3- and 5-positions is then equally probable. In other words the strong activation of the 3-position may depend on the stabilization of the corresponding σ-complex due to mutual conjugation between the heteroatom and the electron-attracting groups.



Substituents such as CO_2Me or NO_2 have strong stabilizing effect on structures such as (VII), (VIII), and (XII), the negative charge being delocalized by the substituents; this also applies to a lesser extent to the halogens (see for instance the effect of chloro- or bromo-substituents on the acidity of phenols); the effect of the methyl group is small.

Even for thiophen in the ground state the presence of electron-withdrawing substituents in the 2-position give rise to some dienic character [see (XIV)] which could explain the preference for attack at the 3-position (the terminal atom of the dienic system).



(XIV)

This kind of explanation is, of course, only qualitative; a complete molecular orbital analysis of the system, necessary for any kind of semiquantitative interpretation, would be particularly difficult, because of the number of heteroatoms involved.

The above theory accommodates the experimental results with the possible exception of that for 2-nitrothiophen. In this case the relative reactivities of the 3- and 5-positions are reversed, phenylation giving 76% of the 3-isomer. It is well known that all substituents exhibit a poorly defined ' *ortho*-orientating effect ' in phenylation reactions; this effect can explain the isomer ratio obtained with 2-methylthiophen, but in the case of nitrobenzene [1] the *ortho* : *para* ratio is only 2·25 (2 *ortho*-positions), and this is inconsistent with product ratios observed for nitrothiophen. The isomer ratio and the very high partial rate factor for the 3-position (see Table 2) observed in this case are probably better interpreted in terms of some kind of direct interaction between the phenyl radical and the substituent which precedes the formation of the α-complex.

Total and partial rate factors for the phenylation of the same thiophen derivatives are reported in Table 2. The more interesting values are k_5 and k_3'; these data reflect the change in reactivity at the α and β positions respectively, induced by the substituent. The values of k_3' were calculated from k_3 (that is the ' experimental ' value obtained from direct analysis of the reaction mixture) using the relation $k_3' = k_3 \cdot \frac{\text{mole (I)}}{\text{mole (II)}}$.

From these data it is seen that the effect of a substituent attached to a benzene nucleus is different from that when it is at the 2 position of a thiophen nucleus.

TABLE 2

Total and partial rate factors for the phenylation of 2-X-thiophen *

X	K_{tot}	% 3	k_3	k_3'	% 4	k_4	% 5	k_5
H	(1·00)		0·07	1·0		0·07		1·00
Me	1·08	16·6	0·36	4·77	4·2	0·09	79·2	1·72
Br	0·61	30·7	0·38	5·05	4·8	0·06	64·5	0·80
Cl	0·53	34·0	0·36	4·77	6·6	0·07	59·4	0·63
CO_2Me	2·26	49·7	2·25	29·89	1·8	0·08	48·5	2·19
NO_2	6·06	77·0	9·30	123·0			23·0	2·80

* Mean values obtained from competitive experiments by using both *N*-nitrosoacetanilide or aprotic diazotization of aniline as radical sources.

The 3-position of 2-methyl-, 2-chloro-, and 2-bromothiophen is *ca.* 5 times more reactive than the corresponding 3-position of the unsubstituted heterocyclic, the k_{ortho} relative to the phenylation of the correspondent benzene derivatives being respectively 2·4, 1·8, and 2·2 (1); k_3' for 2 methylthenoate is 29, while the *ortho* position of methyl benzoate is only 3·0 times more reactive than a single position of benzene.

A surprising result is the deactivation of the 5-position in chloro- and bromo-thiophen. In the benzene series all the substituents examined, if steric effects are not involved, exhibit an activating effect on the nucleus; bromo- and chloro-thiophen are, instead, less reactive than thiophen.

A careful analysis of these two reactions failed to give any evidence against the validity of the competitive ex-

periments; that is, the rate of phenylation is independent of the phenylating agent and the concentration of the substrates. The substitution of the halogen by the phenyl radical in the competitive reaction would lead to an apparent decrease of the rate factors, due to the increased amount of 2-phenylthiophen in the reaction mixture; but the phenylation of bromo- or chlorothiophen in the absence of thiophen does not lead to the formation of 2-phenylthiophen, and the ratio 2 : 3 phenylthiophen in the competitive experiments is 93 : 7, as expected from the known reactivity of thiophen; evidently under our experimental conditions the substitution of the halogen atom, observed in other systems,[7] is not possible.

From the data reported above it is possible to conclude that, at least in the case examined, the substituent effect in the phenylation reaction is not a simple additive property. The reactivity of the 3-position is, in every case, greater than that expected by considering separately the reactivity of the thiophen nucleus and the effect that the substituent exhibits in the benzene series. Furthermore, the presence of halogen seems to deactivate the *para*-like 5-position of the thiophen nucleus. This different behaviour of substituents is not perhaps surprising when it is considered that thiophen is an odd-non-alternant aromatic system and the stabilizing factors in such systems are not expected to be the same as those observed in the even-alternant benzene nucleus.

Before drawing any general conclusion it is, of course, necessary to study the substituent effect in other systems; the reactivity of 3-substituted thiophens towards phenyl radicals is now under examination in our laboratories.

EXPERIMENTAL

Gas-chromatographic analysis and separations were carried out on VARIAN 1520 analytical and VARIAN 712 preparative gas chromatographs, equipped with flame ionization detectors. N.m.r. spectra were measured on a JEOL C60HL instrument.

Thiophen, 2-methylthiophen, 2-bromothiophen, and 2-chlorothiophen were commercial products purified in the usual way; 2-methyl thenoate was prepared by esterification of commercial 2-thenoic acid, and 2-nitrothiophen, obtained by nitration,[8] was purified by the method of Ostman.[9]

Reference Compounds.—2- and 3-Phenylthiophen,[10,11] 3-, 4-, and 5-phenyl-2-methylthiophen,[12,13] 3-, 4- and 5-phenyl-2-bromothiophen,[14,15] the methyl esters of 3-, 4-, and 5-phenyl-2-thenoic acids,[16] 3- and 5-phenyl-2-nitrothiophen [17] and 1,2-di-(2-thienyl)ethane [18] were synthesized as reported in the literature.

2-Nitro-4-phenylthiophen.—2-Nitro-4-iodothiophen (0·5 g.), prepared by nitration of 3-iodothiophen [19] and chromatographically separated from the 2-isomer, was photolysed (Hanau PL 365 high-pressure lamp) in benzene (100 ml.) for 24 hr.

Chromatography on silica gel of the reaction mixture led to separation of 2-nitro-4-phenylthiophen (0·37 g., 94%), m.p. 93—94° (Found: C, 58·65; H, 3·45; S, 15·9; N, 6·9. $C_{10}H_7NO_2S$ requires C, 58·55; H, 3·4; S, 15·6; N, 6·3%).

With the same method were prepared *2-chloro-5-phenylthiophen*, from 2-chloro-5-iodothiophen,[20] m.p. 87—88° (Found: C, 62·0; H, 3·4; S, 16·3; Cl, 18·05. $C_{10}H_7ClS$ requires C, 61·7; H, 3·6; S, 16·45; Cl, 18·25%), and *2-chloro-4-phenylthiophen* from 2-chloro-4-iodothiophen,[21] m.p. 61—62° (Found: C, 61·6; H, 3·75; S, 16·3; Cl, 18·1. $C_{10}H_7ClS$ requires C, 61·7; H, 3·6; S, 16·45; Cl, 18·25%).

2-Chloro-3-phenylthiophen.—To a solution of 3-phenylthiophen (3 g.) in CCl_4 (30 ml.) was slowly added sulphuryl chloride (2·10 g.); the mixture was refluxed for 24 hr. Chromatography of the reaction mixture (silica gel, elution with n-pentane) allowed the separation of 2-chloro-3-phenylthiophen as an oil (2·5 g., 33%), b.p. 128—130 °C/2 mm. (Found: C, 61·5; H, 3·85; S, 17·0; Cl, 18·0. $C_{10}H_7ClS$ requires C, 61·7; H, 3·6; S, 16·45; Cl, 18·25%).

Phenylation Reactions.—The following competitive experiments serve to exemplify the phenylation procedure.

(1) A solution of aniline (3·0 ml.), isopentyl nitrite (6·6 ml.), thiophen (65 ml.), and 2-methylthiophen (80 ml.) was thermostatted at 40 °C, the reaction vessel being a hermetically sealed 200-ml. steel bomb. After 24 hr., the reaction mixture was directly analysed by gas-chromatography using a flame ionization detector, the response of which was calibrated with known mixtures of 2-phenylthiophen and 2-phenyl-5-methylthiophen. Using a $\frac{1}{8}$ in. packed column [5% Bentone 34 + 5% polyphenyl ether (6 rings) on Aeropak 30, 80—100 mesh, 3 ft.] the separation of 2-phenylthiophen (1·03 g.), 3-phenylthiophen (0·08 g.), 1,2-di-(2-thienyl)ethane, 2-methyl-3-phenylthiophen (0·20 g.), 2-methyl-4-phenylthiophen (0·05 g.), and 2-methyl-5-phenylthiophen (0·06 g.) was achieved. The reaction mixture was then carefully concentrated under reduced pressure, and the residue (2 ml.) was injected in 0·25-ml. portions into a preparative gas chromatograph VARIAN 712 equipped with flame ionization detector and a 15% LAC 728 on Aeropak 30 (60—80 mesh) column. Pure samples of 2-methyl-5-phenylthiophen and 2-methyl-3-phenylthiophen were separated and identified; the other peaks were respectively mixtures of 2- and 3-phenylthiophen, and of 1,2-di-(2-thienyl)ethane and 2-methyl-4-phenylthiophen, as demonstrated by i.r. and n.m.r. spectroscopy.

(2) *N*-Nitrosoacetanilide (0·52 g.), thiophen (6·5 ml.), and 2-methylthiophen (8·0 ml.) were thermostatted at 40 °C in the presence of sodium carbonate (0·3 g.), the reaction

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vessel being a hermetically sealed 20-ml. steel bomb. After 24 hr. the reaction mixture was analysed using the same methods reported above: 2-phenylthiophen (0·119 g.), 3-phenylthiophen (0·0091 g.), 1,2-di-(2-thienyl)ethane, 2-methyl-3-phenylthiophen (0·023 g.), 2-methyl-4-phenylthiophen (0·0059 g.), and 2-methyl-5-phenylthiophen (0·111 g.) were identified.

(3) Thiophen (2·45 ml.), 2-methylthiophen (3·0 ml.), and iodobenzene (0·15 ml.) were photolysed in a thermostatted (40 °C) 10-ml. quartz vessel for 24 hr.

Analysis as above of the reaction mixture allowed the identification of 2-phenylthiophen (0·059 g.), 3-phenylthiophen (0·0045 g.), 1,2-di-(2-thienyl)ethane, 2-methyl-3-phenylthiophen (0·0112 g.), 2-methyl-4-phenylthiophen (0·0032 g.), and 2-methyl-5-phenylthiophen (0·055 g.). No dithienyls were identified in the reaction mixture.

With the same methods were carried out phenylation reactions of 2-methylthiophen, 2-chlorothiophen, 2-bromothiophen, methyl 2-thenoate, and 2-nitrothiophen alone or in presence of thiophen in equimolecular proportions. At least 3 independent experiments were carried out for each reaction and the results were reproducible with an error of ±7%.

The mean values obtained in the analysis are reported in the text.

Gas-chromatographic separations were achieved with the following columns, phenylation of chlorothiophen, bromothiophen, and methyl 2-thenoate: 5% FFAP on Aeropak 30 (80—100 mesh), 3 m., $\frac{1}{8}$ in.

In the phenylation of nitrothiophen the thermal instability of the products made the conditions of the analysis critical. Good results with standard samples of nitro(phenyl)thiophens and 2-phenylthiophen were obtained with a $\frac{1}{8}$ in. 5% SE 30 on Aeropak 30 (80—100 mesh) (1 m.) column, by injecting the sample directly on the column. Temperature of the oven: 170 °C; injector: 230 °C; detector: 230 °C.

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