198. *Nucleophilic Reactivity. Part II.* The Reaction between Substituted Thiophenols and Benzyl Bromides.*

By R. F. Hudson and G. Klopman.

The rates of reaction of a series of *para*-substituted thiophenols with several 4-substituted benzyl bromides, and the pK_a values of the thiophenols, in methanol have been measured. The systematic deviations from the Brönsted catalysis law are discussed, and modified reaction constants, ρ_N, are obtained by plotting the rate constants for each bromide logarithmically against the corresponding values for the unsubstituted bromide. The reaction constants increase linearly with the Hammett σ-values for the substituent in the bromide. The significance of this relation is discussed in terms of the charge density at the reaction centre.

Although no general correlation is found between nucleophilic reactivity and basicity towards protons, close correlations are usually observed when the rates of reactions of a series of similar nucleophiles are compared. Thus the Brönsted catalysis law, which was originally applied to general acid–base-catalyses,[1] has been applied successfully to acylation,[2] phosphorylation,[3] and alkylation.[4]

The more general Hammett ρ–σ relation [5] is usually used when aromatic nucleophiles, *e.g.*, phenols and amines, are investigated, although modified σ-constants have to be defined.[6] The σ-parameter, being characteristic of the reactant in which the substitution is made, in the present case the nucleophile, can be related to the charge distribution in the molecule, and hence to the localisation energy.[7] The value of the ρ-parameter, however, depends on the transmission of charge to the reaction centre, the charge density at the reaction centre,[8] and the reaction conditions.[9] It is not surprising, therefore, that the interpretation of ρ-values has been difficult.[9]

In order to investigate the variation of the reaction constant ρ with systematic changes in the transition-state structure, it is necessary to fix the reaction conditions and the nature of the nucleophile, and hence the electronic system through which the charge transmission occurs. The magnitude of ρ should then be related to the charge density at the electrophilic centre [8] and therefore to the reaction mechanism.

In order to determine the change in the reaction constant with a regular change in transition-state structure, the rates of reaction of a series of 4-substituted benzyl bromides with a series of *para*-substituted thiophenols in methanol have been measured polarographically:

$$p\text{-R}\cdot C_6H_4\cdot CH_2Br + p\text{-R}'\cdot C_6H_4\cdot S^- \longrightarrow p\text{-R}\cdot C_6H_4\cdot CH_2\cdot S\cdot C_6H_4R'\text{-}p + Br^-$$

where $R = NO_2$, Br, H, Me, or MeO, and $R' =$ Ac, Cl, Br, F, H, Me, or MeO.

This reaction was chosen for the following reasons: (*a*) The transition-state structure of a benzyl halide is very sensitive to substitution in the aromatic ring,[10] so that the charge density may be varied in a regular way. (*b*) Bromides are more reactive than chlorides and are more stable than the corresponding iodides. (*c*) Thiols are highly reactive, and the reaction of the benzyl bromides with methanol and methoxide ions, introduced to

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* Part I, preceding paper.

[1] Bell, " The Proton in Chemistry," Methuen, London, 1959, p. 155.

[2] (*a*) Bruice and Lapinski, *J. Amer. Chem. Soc.*, 1958, **80**, 2265; (*b*) Bender, *Chem. Rev.*, 1960, **60**, 53.

[3] Green, Sainsbury, Saville, and Stansfield, *J.*, 1958, 1583.

[4] Smith, *J.*, 1943, 521; Green and Kenyon, *J.*, 1950, 1595.

[5] Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 186.

[6] Taft, *J. Phys. Chem.*, 1960, **64**, 1805.

[7] Sixma, *Rec. Trav. chim.*, 1953, **72**, 673; Jaffée, *J. Chem. Phys.*, 1952, **20**, 279, 778, 1554.

[8] Ri and Eyring, *J. Chem. Phys.*, 1940, **8**, 433; Price, *Chem. Rev.*, 1941, **29**, 60.

[9] Jaffé, *Rev. Chem.*, 1953, **53**, 191.

[10] Swain and Langsdorf, *J. Amer. Chem. Soc.*, 1951, **73**, 2813.

maintain the thiols in the fully ionised state, can be neglected. (*d*) Few systematic rate studies have been made with thiols, and the validity of the Brönsted and the Hammett relation for nucleophiles derived from second-row elements has been examined only for substituted phosphines.[11]

Variation in the Structure of the Thiol.—The plots of log *k* against the p*K* value of the corresponding thiol, determined in methanol (p. 1067), show systematic deviations from the Brönsted relation (Fig. 1). Thus the rate of reaction of the unsubstituted thiol is consistently less than that predicted from the optimum straight line, whereas the rate for the *p*-methoxy-compound is uniformly greater. These deviations, which are greater than the experimental errors, show that the various energy factors which contribute to the activation energy [12] are not related in a simple way to the corresponding changes for the combination of the nucleophile with a proton. The origin of these deviations may be illustrated in a general way as follows. Consider the neutralisation to proceed by the following series of processes:

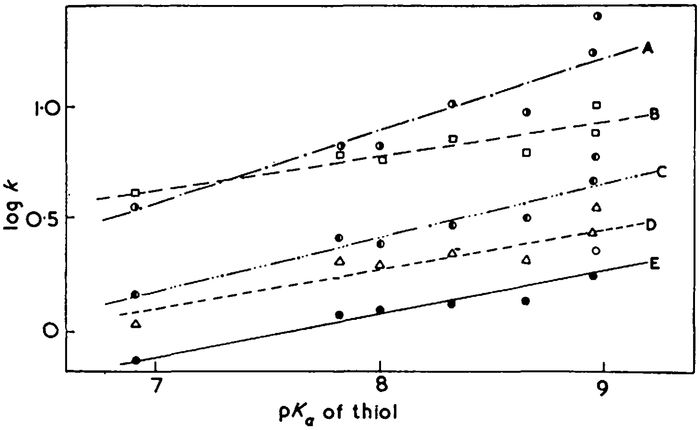

FIG. 1. Plot of log *k* (for reaction of $p\text{-R}\cdot C_6H_4\cdot CH_2Br$ with $p\text{-R}'\cdot C_6H_4\cdot S^-$) against pK_a of the thiol.
R = (A) NO_2, (B) MeO, (C) Br, (D) Me, (E) H.

$$p\text{-R}\cdot C_6H_4\cdot S^- \longrightarrow p\text{-R}\cdot C_6H_4\cdot S + e; \quad E = \Delta H_S + E_S$$
$$H^+ + e \longrightarrow H; \quad E = I + \Delta H_H$$
$$H + p\text{-R}\cdot C_6H_4\cdot S \longrightarrow p\text{-R}\cdot C_6H_4\cdot SH; \quad E = D_{SH}$$

The overall energy of the process is

$$\Delta H = \Delta H_S + E_S - D_{SH} - I + \Delta H_H. \qquad (1)$$

Suppose that substitution proceeds by a stretching of the R–Br bond to the critical separation distance characteristic of the transition state, which requires an energy E_1 followed by a charge transfer *ze* from the nucleophile to $R^{\delta+}$.

$$RBr \longrightarrow R^{\delta+}\text{—}Br^{\delta-} \xrightarrow{N^-} N_z^{(1-z)-}\text{—}R^{(\delta-z)+}\text{—}Br^{\delta-} \longrightarrow NR + Br^-$$

(where N = a nucleophile)

Then the energy required ΔE^* is given by

$$\Delta E^* = \alpha\Delta H_S + \beta E_S - \gamma D_{NR} + E_1. \qquad (2)$$

In this equation, the energy of polarisation of the nucleophile is introduced in the βE_S

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[11] Davies and Lewis, *J.*, 1934, 1599.

[12] Bell, *Proc. Roy. Soc.*, 1936, *A*, **154**, 414; Evans and Polanyi, *Trans. Faraday Soc.*, 1938, **34**, 11.

term as a fraction of the electron affinity, and the repulsion energy between the electrons in the *p*-orbital forming the reaction co-ordinate is included in the bond-energy term D_{NR}.

Substitution in the nucleophile will generally change the terms ΔH_S, E_S, and D_{NR} in a regular way, but not necessarily proportionally. Thus an electron-attracting substituent will increase the electron affinity, decrease the bond energy, and decrease the solvation energy by dispersion of the charge in the nucleophile.

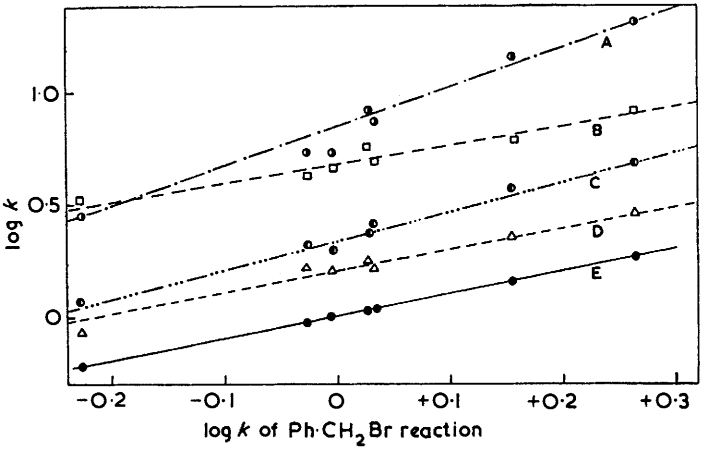


FIG. 2. Plot of log *k* for reaction of p-R·C_6H_4·CH_2Br with p-R′·C_6H_4·S^- against log *k* for reaction of Ph·CH_2Br with p-R′·C_6H_4·S^-.
R = (A) NO_2, (B) MeO, (C) Br, (D) Me, (E) H.

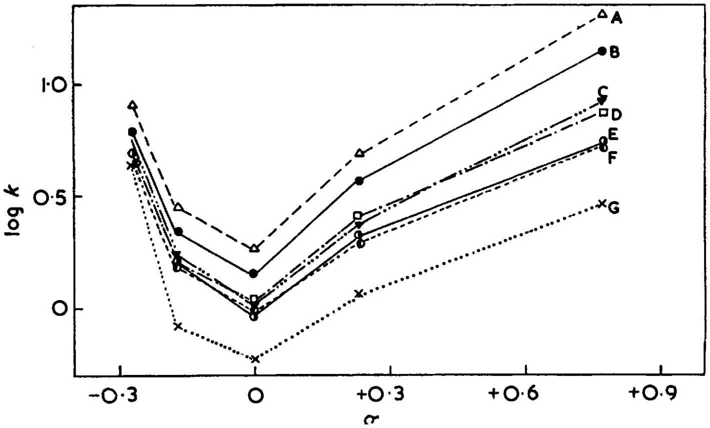


FIG. 3. Plot of log *k* against Hammett's σ-constant for R in p-R·C_6H_4·CH_2Br.
R′ = (A) MeO, (B) Me, (C) F, (D) H, (E) Br, (F) Cl, (G) Ac in p-R′·C_6H_4·S^-.

The electron affinity in the present case may be assumed to be given by the sum of a constant E for the atom S, and the conjugation energy E_c in the ion, *i.e.*, $E_S = E + E_c$.

Comparison of equations (1) and (2) shows that ΔE^* is linear in ΔH, and the Brönsted relation holds, when

$$\Delta H_S = -K_1E_c + \text{Constant and } D_{NR} = -K_2E_c + \text{Constant.} \qquad (3)$$

Deviations from these linear relations will produce the deviations frequently observed in the Brönsted relation (see Fig. 1). (The following conditions also lead to proportionality between ΔE^* and ΔH, but are considered to have no general validity: $\alpha = \beta = \gamma$; $\beta \gg \alpha, \gamma$; or $\gamma \gg \alpha, \beta$. If $\alpha \gg \beta, \gamma$, the Brönsted coefficient is negative.)

When equations (1)—(3) are combined, the Brönsted equation is obtained in terms of the energy changes involved:

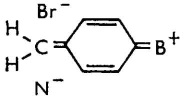
$$\Delta E^* = \Delta H(\alpha + \gamma K_2 - \beta K_1)/(1 + K_2 - K_1) + \text{Constant}.$$

Since ΔH increases as E_c increases, $1 + K_2 - K_1 > 0$; hence for a positive coefficient of the Brönsted relation, $\alpha + \gamma K_2 - \beta K_1 > 0$. Moreover, the coefficients α, γ, and β will increase with the extent of the interaction between the nucleophile and the reaction centre, *i.e.*, with the charge transfer ze, which will increase with a decrease in the electron density at the electrophilic centre. This conclusion is examined in the light of the present experimental data, in the following section.

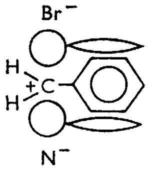
In view of the regular form of the deviations from the Brönsted relation (Fig. 1), a derived relation, with one of the bromides as a reference, may be obtained. Plotting the log k values for the reactions of each bromide with the thiophenols against the log k values for the corresponding reactions of benzyl bromide gives a series of lines of varying slope (Fig. 2). The slopes give a reaction parameter ρ_N, which has a similar significance to the Brönsted coefficient, since it is a measure of the sensitivity of the rate of reaction to changes in charge distribution in the nucleophile.[6]

Variation in the Structure of the Bromide.—If the log k values are plotted against the Hammett σ functions for the different substituents in the bromide, a series of curves identical in form is obtained for each nucleophile (Fig. 3). Both electron-attracting and electron-donating substituents increase the reactivity, suggesting that a gradual change in mechanism occurs, as discussed in detail by Swain and Langsdorf[10] in terms of the relative importance of bond-making and bond-breaking in the transition state.*

Thus electron-donating substituents conjugate with the incipient carbonium ion, reducing the interaction with the nucleophile and the leaving group, as represented by structure (I). On the other hand, electron-attracting substituents may promote conjugation between the π-orbitals of the benzene ring and the pseudo-π p-orbital,[13] as represented by (II). This increases the interaction energy with the nucleophile, and hence the bond-forming energy. The relative importance of these structures is represented by the Hammett σ-value, which is usually taken to give a quantitative measure of the decrease in electron density at the reaction centre.[9]



(I)



(II)

According to the interpretation of the reaction given in the previous section, the reaction parameter ρ_N should increase regularly with the decrease in electron density at the reaction centre, a conclusion which is supported by the linear increase in ρ_N with σ (Fig. 4). Such a relation is inferred in the various interpretations of the Hammett relation,[9] but this is probably the first direct demonstration involving a systematic variation in the nucleophile. The limited work of Williams and Hinshelwood[14] on the

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* It was pointed out by a Referee that Brown σ^+ values may be more suitable than σ constants for the effect of substituents in displacement reactions at a saturated carbon atom. Significant variations from linearity could then be attributed to the influence of the bond-making process. The forms of the log k–σ and log k–σ^+ curves are, however, very similar, so that the introduction of $\sigma^\pm$ values does not affect the interpretation in terms of a variation of transition-state structure with substitution in the bromide.

[13] Dewar, "Electronic Interpretation of Organic Chemistry," Oxford Univ. Press, 1949, p. 73; Daudel and Chalvet, *J. Chim. phys.*, 1956, 943.

[14] Williams and Hinshelwood, *J.*, 1934, 1079.

reaction between substituted anilines and substituted benzoyl chlorides (Table 1) show a similar change in ρ_N (represented by the ratio of the rate constants for the reaction with aniline and *p*-nitroaniline in Table 1) with σ for the substituent in the benzoyl chloride.

TABLE 1.

Rates of reaction between *p*-$R\cdot C_6H_4\cdot COCl$ and *p*-$R'\cdot C_6H_4\cdot NH_2$ in benzene at 25°.

R	R′ = H	R′ = NO_2	$10^3k_H/k_{NO_2}$	σ	ρ
NO_2	58·1	0·0097	5·99	0·78	3·2
H	6·88	0·0042	1·64	0	2·7

The changes in k_H/k_{NO_2} are relatively small in this case which may be due to the high charge transfer *ze* on formation of the transition state, which probably resembles the tetrahedral intermediate.[25] This view is supported by the high values of the Brönsted coefficient ($\alpha \approx 0{\cdot}8$—$1{\cdot}0$) for various acylations.[2] If bond formation is essentially complete in the transition state, changes in the electronic distribution in the reactant containing the electrophilic group will probably have a small effect on the transition-state structure.

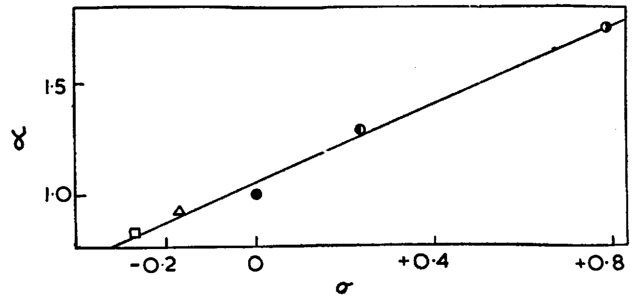

FIG. 4. Plot of ρ_N against Hammett's σ-constant for the substituent (points reading right to left: NO_2, Br, H, Me, MeO).

EXPERIMENTAL

Preparation and Purification of the Products.—A methanolic solution of lithium methoxide was prepared by the action of fresh lithium on absolute methanol (" Fluka "). A sample was titrated with 0·1N-hydrochloric acid, and the remainder diluted to give a 0·25N-solution. The substituted benzyl bromides (" Fluka " puriss.) were recrystallised or redistilled before each series of experiments. 4-Methoxybenzyl bromide was prepared by bubbling hydrogen bromide through a solution of the alcohol in benzene.[15] The following thiophenols were used: *p*-methoxy-, b. p. 70—71°/0·8 mm.; *p*-methyl-, m. p. 42—43° [from light petroleum, (b. p. 60—80°)]; and *p*-chloro-thiophenol, m. p. 51—53° [from light petroleum (b. p. 60—80°)]; thiophenol, b. p. 60°/15 mm. *p*-Fluorothiophenol, b. p. 52—53°/14·5 mm., was prepared by reduction with zinc and hydrochloric acid of the adduct of sulphur and the Grignard reagent obtained from magnesium and *p*-bromofluorobenzene.[16] *p*-Bromothiophenol was prepared by reduction with zinc in hydrochloric acid of *p*-bromobenzenesulphonyl chloride, and purified by steam distillation and recrystallisation from light petroleum (b. p. 60—80°), m. p. 74—75°.

p-Acetylthiophenol, prepared by the action of ethyl xanthate on diazotised *p*-aminoacetophenone, followed by saponification of the product,[17] had b. p. 84—87°/0·15 mm.

Rate Measurements.—In view of the high rates of reaction, rapid polarography was used.[18] Each bromide gave a cathodic wave at approximately −1·2 v,[19] the height of which was proportional to concentration in each case, thus enabling the change in the bromide concentration with time to be followed.

The thiophenols give an anodic wave around −0·4 v, which does not interfere with the

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[15] Lapworth and Shoesmith, *J.*, 1922, **121**, 1391.
[16] Muvaffak, Seyhan, and Aksu, *Ber.*, 1939, **72**, 594.
[17] Riesz and Frankfurter, *Monatsh.*, 1928, **50**, 72.
[18] Wolf, *Angew. Chem.*, 1960, **13**, 449.
[19] Klopman, *Helv. Chim. Acta*, 1961, **44**, 1908.

cathodic wave. The detailed procedure for measuring rates of reaction in methanol containing 0·25M-lithium methoxide has been described elsewhere.[20]

The reaction between the bromide and the methoxide ion [20] could be neglected, except in the case of 4-methoxybenzyl bromide, for which the appropriate adjustment to the measured rate was made.

Results.—The rate constants were obtained in two ways.

(*a*) At least six independent experiments were made at 20·0° and the mean values of the rate constants and their maximum deviations were calculated (Table 2). For example, in the reaction between thiophenol and 4-methoxybenzyl bromide, the following values were obtained: 4·82; 4·92; 4·86; 4·92; 5·15; 4·88. Mean value = 4·93 ± 0·12 l. mole^{-1} sec.$^{-1}$.

(*b*) In other cases, the measurements were made at a series of temperatures within the 5—25° range, and the logarithm of the rate constant was plotted against the reciprocal of the absolute temperature. The value at 20·0° was then obtained by interpolation, as shown by the following values for the reaction between *p*-chlorothiophenol and 4-bromobenzyl bromide:

Temp. (°C)	5·8	8·9	12·3	14·0	18·6	24·8	(20)
10^3/Temp. (°K)	3·584	3·545	3·503	3·482	3·427	3·356	3·411
log *k*	−0·229	−0·114	+0·015	0·085	0·246	0·464	0·296

A summary of the rate constants is given in Table 2.

TABLE 2.

Rate constants (l. mole^{-1} sec.$^{-1}$) for the reactions between 4-substituted benzyl bromides and aromatic thiols at 20° in methanol.

	Bromide				
Thiols	4-MeO	4-Me	H	4-Br	4-NO_2
p-MeO	8·15	2·85	1·84	4·80	20·8
p-Me	6·13	2·23	1·43	3·70	14·0
H	4·93	1·63	1·08	2·57	7·49
p-F	5·69	1·75	1·02	2·39	8·13
p-Cl	4·62	1·56	0·99	1·98	5·31
p-Br	4·83	1·64	0·94	2·08	5·39
p-Ac	3·28	0·85	0·59(3)	1·17	2·83
α-Naphthyl	8·77	2·29	1·57	3·86	10·74
β-Naphthyl	8·77	2·43	1·51	3·78	9·55

Measurements of pK_a *of Thiophenols in Methanol.*—pK_a's were obtained from the titration curves of 0·005N-solutions of thiophenols in methanol (20 ml.) and 0·2M-solutions of sodium methoxide in methanol, in a stream of nitrogen, by means of a " Radiometer titrograph," Type SBR2/SBUI/TTA2 with a glass electrode (Radiometer 6202 B), resistant to alkali. pK_a values recorded in Table 3 were obtained from the points of half-neutralisation. These values are compared in Table 3 with those given by Schwarzenbach [21] for the same derivatives in 95% aqueous ethanol.

TABLE 3.

pK_a values for *para*-substituted thiophenols in methanol.

Subst.	Concn. (10^{-3}M)	pK_a	pK_a (mean)	pK_a (in 95% EtOH) [21]	Subst.	Concn. (10^{-3}M)	pK_a	pK_a (mean)	pK_a (in 95% EtOH) [21]
MeO	2·18	8·93	8·95 ± 0·02	9·76	Cl	2·47	7·91	8·00 ± 0·09	8·45
	2·84	8·97				3·71	8·04		
Me	2·55	8·85	8·96 ± 0·10	9·70		1·98	8·06		
	2·32	8·98			Br	2·53	7·68	7·82 ± 0·16	8·37
	2·30	9·06				3·29	7·75		
H	2·15	8·62	8·65 ± 0·05	9·32		2·03	7·98		
	2·15	8·62			Ac	2·14	6·96	6·91 ± 0·08	7·28
	3·04	8·70				2·78	6·83		
F	2·44	8·32	8·32 ± 0·02			3·42	6·95		
	3·66	8·30							
	3·26	8·34							

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[20] Hudson and Klopman, *Helv. Chim. Acta*, 1961, **44**, 1914.

[21] Schwarzenbach, *Helv. Chim. Acta*, 1939, **22**, 360.