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NATURE AND COMPOSITION OF *ORTHO*-EFFECT

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Second-order rate constants and activation parameters for the reaction of phenacyl bromide with *ortho*-substituted anilines were measured in methanol. The linear multiple regression analysis has been applied to the study of the effect of substituents on this reaction. The results support the conclusion of Charton that the effect of the *ortho*-substituents is primarily electrical. The methyl substituent behaves in an unique way.

INTRODUCTION

The *ortho*-effect is a proximity effect which occurs when substituent and reaction site are bonded to adjacent atoms in an aromatic ring. The *ortho*-effect may be dissected into three possible major contributions, electrical effects, steric effects and intramolecular secondary bonding forces.[1] When the side chain becomes sufficiently large the substituent and the reaction site are no longer sufficiently close to each other to permit the existence of the proximity effect. Among the numerous attempts to understand the nature and composition of *ortho*-effect, those of Taft[2], Charton,[1], Farthing and Nam[3] and Chapman and Shorter[4] have met with varying degrees of success. The approach proposed by Fujita and Nishioka[5] is claimed to be promising one by Geovanni Consiglio *et al.*[6] However, Charton's findings and conclusions seem to be remarkable to us even though Mager *et al.*[7] differ from Charton's approach. The aim of this work is to verify that the effect of the *ortho*-substituent is primarily electrical in the reaction chosen. In the present investigation, the S_N2 reaction of phenacyl bromide with *ortho*-substituted anilines are analysed. A systematic study and multiparameter linear regression analysis on the influence of *ortho*-substituent on this reaction have been reported in this paper.

EXPERIMENTAL

Methods and Materials

Aniline, *o*-toluidine, *o*-chloroaniline, *o*-anisidine, *o*-aminoacetophenone and *o*-aminobenzoic acid were commercial samples which were purified by repeated distillation or recrystallization. *o*-Phenetidine, *o*-iodoaniline, *o*-bromoaniline and phenacyl bromide were prepared by the best available procedures. The physical constants of all these compounds agreed well with the values reported in the literature. Methanol B.D.H.AnalaR grade was used as such without further purification.

Rate measurements—The rate measurements were carried out in methyl alcohol at three temperatures 30°, 35° and 40°C. The thermostated (± 0.01°)

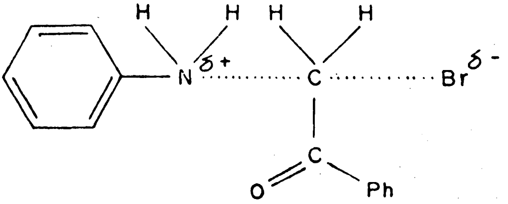
solutions of phenacyl bromide (0.125 M) and anilines (0.25 M) were mixed. The course of the reaction was followed by pipetting out 2 ml of the reaction mixture at different intervals of time, adding it to (0.025 M) silver nitrate solution (5 ml) to precipitate silver bromide and estimating the excess of silver nitrate with standard ammonium thiocyanate (0.0125 M) using ferric alum as the indicator. The second order rate constant k_2 was evaluated using the equation

$$k_2 = \frac{2.303}{t-(a-b)} \log \frac{b(a-x)}{a(b-x)}$$

It was observed by duplication that the rate constant could be reproduced with an accuracy of ±3%.

RESULTS AND DISCUSSION

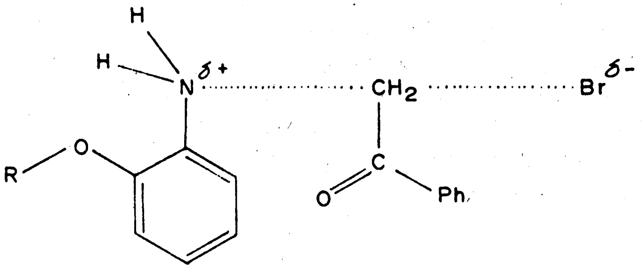
The rate constants for anilino-debromination by *ortho*-substituted anilines in methanol are determined at 30°, 35°, and 40° and the results are presented in Table 1 along with Arrhenius parameters. The thermodynamic parameters are evaluated in the usual way. Based on the results obtained by Rout *et al.*[8] on the anilino-debromination of phenacyl bromide, the most probable mechanism is said to be a direct S_N2 displacement of bromine. In the transition state of this concerted nucleophilic substitution process a positive charge is assumed to develop on the amino nitrogen as shown in I.



I

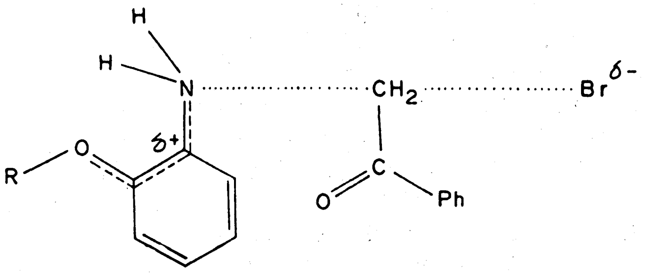
In general *o*-substituted anilines react slowly compared to the corresponding *p*-substituted anilines.[8,9] Among all the *p*-substituted anilines *p*-nitroaniline is least reactive; but *o*-nitroaniline is so inert that it did not undergo this reaction in our hand even when the concentration and temperature of the reaction were increased to practically feasible extent. However, Rout *et al.*[8] reports a rate constant value of 1.157×10^{-2} litre $\text{mol}^{-1}\,\text{min}^{-1}$ for *o*-nitroaniline at 40°. Another notable variation in the *ortho*-series is that *o*-toluidine is less reactive than aniline whereas *p*-toluidine is more reactive. It is significant to note that the CH_3 group acts as a rate-retarder even though it can act as electron-donor by inductive and hyperconjugative mechanisms. But alkyl substituents produce only small electrical effects.[10] Hence, in this situation, perhaps, the primary steric effect may outweigh the electrical effect and this may account for the lower reactivity of *o*-toluidine. All *o*-halogenoanilines are less reactive than aniline and their reactivities are almost the same. We attribute the influence of the *ortho*-alkyl group mainly to primary steric effect, but that of *ortho*-halogen to the electron-withdrawing polar effects operating more strongly from the *ortho*-position than from the *para*-position.[11]

o-Anisidine and *o*-phenetidine are less basic than aniline. There are two opposing polar effects here, viz., +I and –M effects of the alkoxyl group. According to Ingold[12] the +I effect of the *ortho*-alkoxyl group usually outweighs the -M effect and hence one would expect these compounds to be less reactive than aniline. However, it is not so. This observation can very well be explained on the basis of the phenomenon of steric enhancement of resonance. It is now well established [13–16] that a substituent *ortho* to an alkoxyl group in benzene ring does not sterically inhibit the conjugation of the alkoxyl group with aromatic nuclei but enhances it. In the reactions of *o*-anisidine or *o*- phenetidine with phenacyl bromide the amino function becomes more crowded in the transition state and the alkoxyl group takes a preferred orientation as shown in II. The free rotation of the RO- is restricted and it is more coplanar with the benzene ring.



II

OMe and OEt have much smaller steric effects than Me; no doubt they can rotate away from the reaction centre.[17] In this geometry the lone pair orbital of oxygen is parallel to the *p*-orbital of aromatic carbon which leads to an effective delocalization of the positive charge on the amino nitrogen as shown in III.



III

This delocalization leads to the stabilisation of the transition state resulting in the rate enhancement. The considerably diminished reactivity of anthranilic acid and *o*- acetylaniline can be attributed to the powerful +I and +M effects of the –COOH and –CO.CH_3 groups from the *o*-position. The effect of chelation of these groups with the amino function leads to resonance stabilization of the ground state which in turn results in additional rate retarding effect.

From the experimental data (Table 1) the *ortho*-substituted anilines can be arranged in the decreasing order of reactivity as follows:

o-phenetidine > *o*-anisidine > aniline > *o*-toluidine
o-chloroaniline ≈ *o*-bromoaniline > *o*-iodoaniline
o-aminobenzoic > *o*-acetylaniline

The plot between the rate constants and pK_a values of the conjugate acid of the anilines is not linear indicating the failure of Bronsted relationship. This failure may be due to the different effect of the *o*-substituents separately influencing rate and acidity. Moreover, basicity is thermodynamically controlled and reactivity is kinetically controlled.

TABLE 1
SECOND-OREDR RATE CONSTANTS AND THERMODYNAMIC PARAMETERS FOR THE REACTION BETWEEN *o*-SUBSTITUTED ANILINES AND PHENACYL BROMIDE IN METHANOL

o-substituent	$k_2 \times 10^2$ litre mol^{-1} min^{-1}			E_a kcal mol^{-1}	$\Delta H^{\neq}$ kcal mol^{-1}	$-\Delta S^{\neq}$ e. u	log *PZ*
	30°	35°	40°				
OC_2H_5	6.90	9.37	12.12	10.6	10.0	38.4	6.4
OCH_3	6.59	8.73	10.81	9.3	8.7	43.4	5.5
CH_3	2.11	2.82	3.65	10.3	9.7	42.3	5.7
H	3.50	5.04	6.74	12.3	11.7	34.6	7.4
Cl	0.205	0.256	0.364	12.2	11.5	40.9	6.0
Br	0.209	0.262	0.389	13.4	12.8	36.2	6.9
I	—	0.245	0.356	14.3	13.7	33.9	7.5
COOH	0.110	0.180	0.284	17.9	17.3	23.3	9.9
$COCH_3$	0.061	0.090	0.124	13.3	12.7	39.5	6.3

Thermodynamic parameters

The electron-donating substituents (halogens exception) have lower energy of activation whereas electron-withdrawing substituents have higher energy of activation. The enthalpy of activation, $\Delta H^{\neq}$ shows a regular variationn in that the electron-donating groups decrease $\Delta H^{\neq}$ whereas the other types increase. This is in consistent with the assumption that the $\Delta H^{\neq}$ reflects the repulsive energies between the reactants as they are brought closer together.[18]

An analysis of the entropy values given in Table 1 leads to interesting conclusions. In general, this series is manifested by high negative entropy of activation. The large negative entropy of activation is expected for bimolecular reactions with highly polar transition state. Moreover, in this case the transition state is more crowded compared to the ground state. Both these factors are responsible for higher negative values of entropy. The variation in $\Delta S^{\neq}$ that occurs with distant substitution is believed to be the consequence of the differences in the degree of solvation of the ground state. On the other hand, with the substituent in the close proximity of the functional group, the bulk effect of the substituent will affect the entropy values. Generally, a bulky substituent near the reaction centre will reduce the number of energy levels available to the transition state (which is more crowded) to those in the initial state and this renders $\Delta S^{\neq}$ more negative.[19] For the anilines with the electron-releasing groups (CH_3, OCH_3 and OC_2H_5) in the *ortho*-position, the $\Delta S^{\neq}$ is significantly high. This observation clearly indicates that the transition states are more crowded and rigid in these cases. There is a greater loss of degrees of freedom compared to other cases when the molecule goes to the transition state. In the case of *o*-halogeno-anilines a regular change in entropy is not observed which makes rationalisation difficult. Anthranilic acid has unusually low negative entropy change. This may be probably due to the effect of chelation. In the ground state, the –COOH has entered into chelation with amino function and the chelation may be disturbed in the transition state by the attack of phenacyl bromide and solvent molecule.

The values of activation parameters are compatible with the above picture. In general, on going from aniline to *ortho*-substituted anilines $\Delta H^{\neq}$ increases while $-\Delta S^{\neq}$ decreases indicating some steric strain in the transition state. A linear relationship between both these parameters has been found for the reaction between *o*-substituted anilines and phenacyl bromide. The result of this correlation indicates that the reaction mechanism is constant in this series, as it is required in order to correctly apply linear free energy relationship.[20] The isokinetic relationship in this case was also examined by correlating log k_2 for 35° and log k_2 for 40° by least squares method[21] ($r = 0.992$). From the value of slope (0.9655) the isokinetic temperature was found to be 575°K. Our reaction temperatures are much below the isokinetic temperature so that the substituent effects on the rate constants are as anticipated.

Linear Free Energy Relationships

From the accepted structure of the transition state (I) one can come to the conclusion that the reaction centre (when aniline is considered as the substrate) is in close proximity with the *o*-substituent in aniline moiety. This indicates that the primary steric effect is expected to play a prominent role in this reaction. This is true in the case of the anilino-debromination of 2-bromo-3,5-dinitrothiophen in which the transition state is much more crowded than that of the present system since aromatic nuclear bromide is being replaced.[6]

But quite contrary to this, there exists only a non-linear correlation in the plot of log (k/k_{Me}) or log (k/k_H) against E_s, the assumed steric parameter of the *ortho*-substituents. The parameters used for correlation are shown in Table 2. We correlated the logarithms of the rate constants for the anilino-debromination of phenacyl bromide by the following Hammett equation.

$$\log k_2 = \log k_2^0 + \rho\sigma_0 \qquad (1)$$

The data from Table 2 have been fitted to Eq. (1) by the least squares analysis to yield the following result:

$$\log k_2 = -1.787 - 2.522\sigma_0 \quad (r = 0.900) \tag{2}$$

TABLE 2

STERIC AND POLAR PARAMETERS FOR *ORTHO*-SUBSTITUENTS[a] AND THE KINETIC DATA[b]

Substituent	$\log\frac{k}{k_H}$ 40°	$\log\frac{k}{k_{CH_3}}$ 40°	E_s	σ_0	σ_0^*
OC_2H_5	+0.255	+0.521	+0.90	—	—
OCH_3	+0.205	+0.472	+0.99	–0.39	–0.22
CH_3	–0.266	0.00	0.00	–0.17	0.00
H	0.00	–0.266	—	0.00	—
Cl	–1.268	–1.001	+0.18	+0.20	+0.37
Br	–1.239	–0.972	0.00	+0.21	+0.38
I	–1.277	–1.011	–0.20	+0.21	+0.38

[a]Ref. (4), p. 76 [b]Present work

But when similar correlation analysis was done on Eq. (3) using σ_0^* (Table 2),

$$\log k_2 = \log k_{Me} + \rho^*\sigma_0^* \tag{3}$$

the result is

$$\log k_2 = -1.486 - 2.498\sigma_0^* \quad (r = 0.999) \tag{4}$$

So the latter analysis shows an excellent correlation giving a value of –2.498 for the polar reaction constant (ρ^*). This indicates that the reaction conforms with Taft's[2] linear polar energy relationship. The negative value of ρ^* reveals that the reaction is facilitated by the electron-repelling substituents in aniline. This is in accordance with the Taft's overall observations on *ortho*-substituted anilines and benzoic acids.[22,23] In this series it may be concluded, from this uniparameter correlation itself, that the steric effect must either be constant, negligible or non-existent. It is also noteworthy that the points obtained by plotting the log k_2 values estimated by using Eq. (4) and the log k_2 values observed fall on the 45° line.

The multiple regression analysis has been exploited as a powerful stastistical tool for the evaluation of structure-reactivity data. One goal of these analyses is the derivation of a regression equation which will provide estimates of some reaction constants, the magnitude of which will reflect the relative importance of the different components of substituent effect, viz., resonance, inductive and steric effects. Charton[1] has correlated 269 sets of reactivity data for *ortho*-substituted compounds using Eq. (5):

$$Q = \alpha\sigma_I + \beta\sigma_R + \Psi r_v + h \tag{5}$$

where Q may be log k or log K (or an observed property under the influence of *ortho*-substituent), α, β and Ψ are the succeptibility constants and h is the intercept and these are determined by the method of least squares. When the steric effect is considered to be zero, the Eq. (5) becomes

$$Q = \alpha\sigma_I + \beta\sigma_R + h \qquad (6)$$

The present data in Table 1 on the anilino-debromination reaction are subjected to such a linear multiple regression analysis and the reaction is found to correlate to dual Hammett substituent parameter treatment. In this analysis the σ_I constants required have been taken from the compilation of Charton[24] and σ_R constants are obtained from the equation (7), σ_P values are taken from the excellent tabulation of McDaniel and Brown.[25]

$$\sigma_p = \sigma_R + \sigma_I \qquad (7)$$

The values used in the present computation are presented in Table 3.

TABLE 3

SUBSTITUENT CONSTANTS AND KINETIC DATA USED IN THE CORRELATION

Substituent	logk_2^d at 40°	σ_I^a	σ_p^b	σ_R	σ_I^c	σ_R^c
OC_2H_5	–0.9165	+0.27	–0.24	–0.51	—	—
OCH_3	–0.9662	+0.25	–0.27	–0.52	+0.31	–0.63
CH_3	–1.4377	–0.05	–0.17	–0.12	–0.06	–0.07
H	–1.1713	—	—	—	0.00	0.00
Cl	–2.4389	+0.47	+0.23	–0.24	+0.51	–0.35
Br	–2.4101	+0.45	+0.23	–0.22	+0.50	–0.34
I	–2.4486	+0.39	+0.27	–0.12	+0.43	–0.23
COOH	–2.5467	—	—	—	+0.34	+0.37
$COCH_3$	–2.9052	—	—	—	+0.34	+0.39

[a] Ref. (24) [b] Ref. (25) [c] Ref. (4) p. 37 [d] Present work

The functional relationship was made by linear multiple regression analysis. The kinetic data at 40° in Table 3 consisting of a set of nine data points, have been fitted by the ordinary least squares analysis employing a calculator to yield the following results:

$$Q = \log k_2 = -2.945\sigma_I - 1.964\sigma_R - 1.429 \qquad (8)$$

with a multiple correlation coefficient, R = 0.834 and standard deviation of R, s = 0.41. But, when the data on the methyl sustituent is excluded from the regression analysis an excellent regression is obtained which fits into the equation,

$$\log k_2 = -3.89\sigma_I - 2.300\sigma_R - 1.138 \qquad (9)$$

with a multiple correlation coefficient R = 0.994 and standard deviation s = 0.10 which predicts the log k_2 value within 0.07 unit of the experimental values in most cases. The plot of log $k_{2\,est}$ and log $k_{2\,obs}$ gives points most of which fall in the 45° line indicating that the estimation and observation are in good agreement (Fig. 1). The regression analysis was also attempted using the σ_I and σ_R values, corrected and recalculated by Exner[26] (Table 3). Here again, the correlation is better when the methyl substituent is deleted from the analysis. Including methyl substituent:

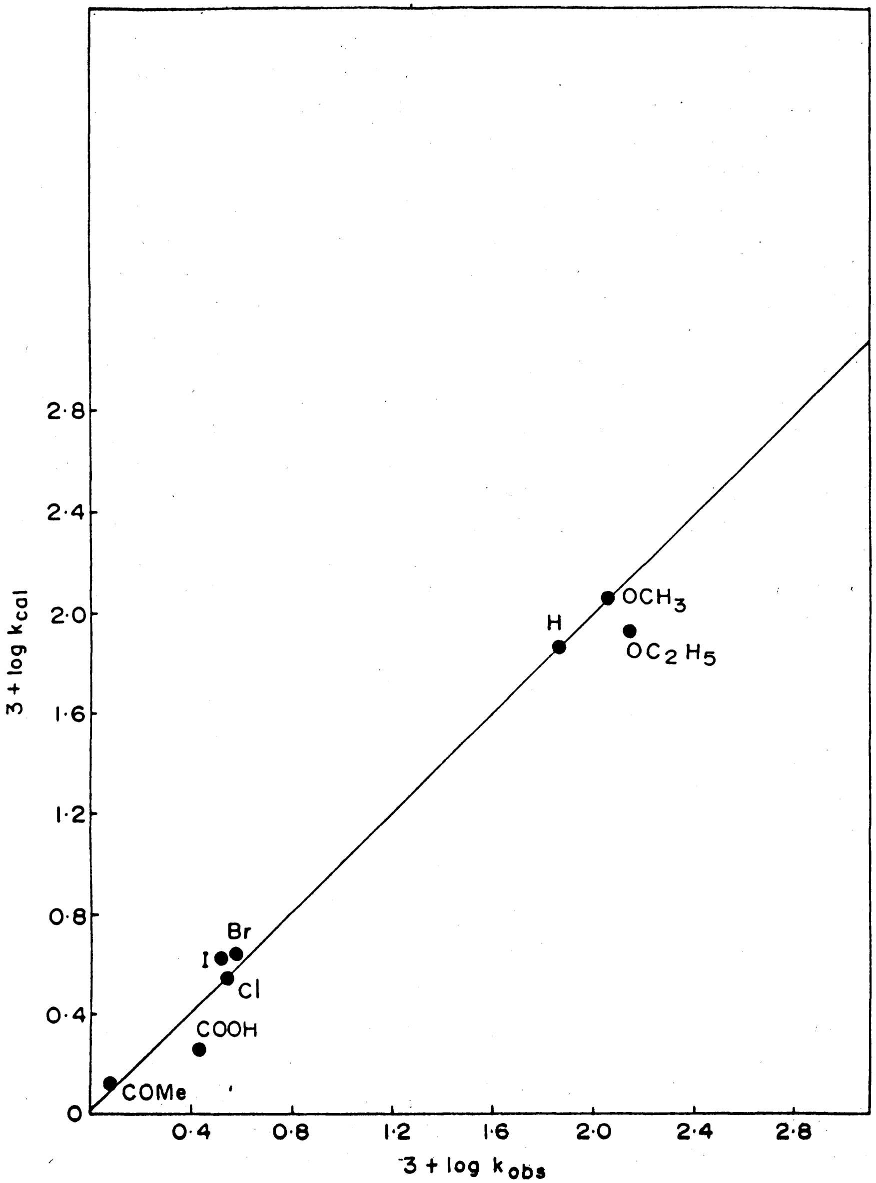


Fig. 1 Plot of log k_{cal} versus log k_{obs}.

$$Q = \log k = -3.505\sigma_I - 2.5613\sigma_R - 1.471 \quad (10)$$

with $R = 0.967$ and $s = 0.22$.

Excluding methyl substituent:

$$Q = \log k = -4.2785\sigma_I - 2.5664\sigma_R - 1.167 \quad (11)$$

with $R = 0.993$ and $s = 0.11$

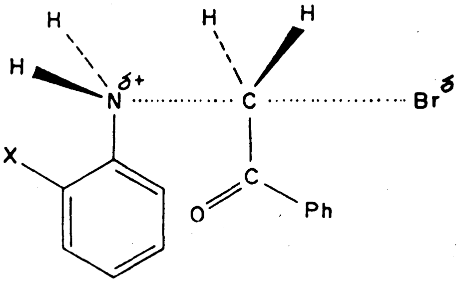
The success of the correlation with equations (9) and (11) seems to support the Charton's^2 conclusion that steric effect is an unimportant component of the *ortho*-effect. The most important results of the correlation analysis are:

(i) The steric effects play a minor role in the *ortho*-effect and only electrical effects are required to account for the substituent effects in this series.

(ii) Quantitative evidence is provided that the *ortho*-substituent effect is mainly a combination of σ_I and σ_R.

(iii) The inductive components are more important relative to resonance components of the *ortho*-substituent constants in this series. The values of ε (= β/α) is the measure of the relative importance of inductive and resonance components.For the present reaction system the values of ε is equal to 0.6 [either from Eq. (9) or (11)] indicating the predominant contribution of the inductive effect to the *ortho*-substituent effect.

(iv) The precision of the correlation is decreased when the methyl substituent is included for the analysis. Among the electron-releasing groups only methyl group is rate-retarding. These observations are very significant. An understanding of the precise geometry and conformation of the transition state may account for the unusual behaviour. The phenacyl bromide molecule attacks the nitrogen of the aniline by coordinating with the lone pair orbital of nitrogen from the side *anti* to that of the *o*-substituent. The transition state is assumed to have the geometry IV.



IV

In this geometry the *o*-substituent may be in a staggered disposition in between the two amine hydrogens. This orientation of the amine hydrogens may be perhaps favoured when X (in IV) is a group other than CH_3 group because all other substituents are possessing some hereto atom (with lone pair of electrons) which can have feeble attraction for the slightly acidic amine hydrogens. But in the case of methyl substituent Van der Waals repulsive forces outweigh any other effect. An examination of Dreiding model of the transition state indicates that there is a slight overlap between the *o*-methyl hydrogens and amino hydrogens.

This view may account for the lower reactivity of *o*-toluidine compared to aniline at all temperatures studied.

TABLE 4
SUBSTITUENT CONSTANTS AND KINETIC DATA[a] USED IN THE CORRELATION FOR *P*-SUBSTITUTED ANILINES

Para-substituent	$k_2 \times 10^2$ at 40° litre mole^{-1} min^{-1}	$\log k_2$	σ_I^b	σ_R
CH_3	5.52	−1.2581	−0.05	−0.12
Cl	1.74	−1.7594	+0.47	−0.24
H	2.76	−1.5591	0.00	0.00
COOH	0.478	−2.3206	+0.34[c]	0.11
NO_2	0.0144	−3.8416	+0.70[c]	0.02

[a]Ref. (8) [b]Ref. (24) [c]Ref. (4), p. 37

A dual parameter linear regression analysis was performed on the kinetic data (five numbers) collected from literature (Table 4)[27] on the *p*-substituted anilines. It resulted in the correlation equation (14).

$$\log k = -2.5970\sigma_I - 2.2313\sigma_R - 1.478 \qquad (12)$$

with $R = 0.929$, $s = 0.49$

Here the correlation is slightly worse than that of *ortho*- analogue. However, the immediate significance is the value of ε ($= \beta/\alpha$), which is approximately equal to 0.9. This indicates that the operation of the resonance effect from the *p*-subsitutuents is in a greater extent when compared to that from the *o*-substituents. The ε_0 (of *ortho*-series) and ε_p (of *para*-series) are related as $\varepsilon_0 = \varepsilon_p \times 0.7$. This is in agreement with the findings of Charton.[28] The general conclusions arrived at from the present correlation analysis are:

(i) The results of this investigation do support the conclusion of Charton that the effect of *ortho*-substituents is primarily electrical.

(ii) The inductive effect of the *ortho*-substituent is much more important than resonance one for this reaction.

(iii) The inductive components are more important relative to resonance components of the substituent effects for *ortho*- than for the *para*-substituents.

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