

## Quantitative treatment of the ortho-effect in reactions of ortho-substituted phenylmercaptoacetic acids

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**Abstract.** The kinetics of oxidation of ortho-substituted phenylmercaptoacetic acids by bromamine T and metaperiodate ion and also the  $pK_a$  values of these acids have been studied. Regression analyses of the rate and equilibrium data indicate that the ortho-substituent effect can be explained by the electrical effects alone, and that in these acids when the reaction site is in close proximity to the ortho-substituent or not, the steric effect is insignificant. The rates of oxidation and the ionization constants of these acids are largely controlled by the inductive effect.

**Keywords.** ortho-substituted phenylmercaptoacetic acids; regression analyses; oxidation kinetics.

### 1. Introduction

The quantitative treatment of the ortho-effect by means of the linear free energy relationship (LFER) is an enigma compared to the far more successful treatment of meta- and para-substituent effects in aromatic systems. The first major attempt to extend LFER correlation to the ortho-effect was due to Taft (1952, 1956). According to Taft, for cases where only polar effects operate (1) holds good, while (2) is applicable for systems where only steric effects operate.

$$\log k_{\text{ortho}} = \rho^* \sigma_0^* + h, \quad (1)$$

$$\log k_{\text{ortho}} = \delta E_s + h. \quad (2)$$

In the above equations,  $\sigma_0^*$  (polar) and  $E_s$  (steric) are the substituent constants,  $\rho^*$  is a reaction constant and  $\delta$  is a steric susceptibility constant. But Taft's  $E_s$  steric parameter is not correctly defined as it is impossible to have steric effects of substituents operating without the concomitant intervention of electronic effects of ortho-substituents. On the basis of statistical analysis, Charton made significant contributions to the quantitative treatment of the ortho-effect (Charton 1971) and he successfully separated the polar effect of an ortho-substituent into inductive and resonance contributions through a dual-parameter treatment,

$$\log k_{\text{ortho}} = \alpha \sigma_1 + \beta \sigma_R + h. \quad (3)$$

In the above equation,  $\alpha$  and  $\beta$  define the relative importance of the inductive and resonance effects, i.e. susceptibility constants, and  $h$  is the intercept.  $\sigma_1$  and  $\sigma_R$  are

\*For correspondence.

the inductive and resonance substituent constants. To account for the steric effect of the substituent an additional term was introduced,

$$\log k_{\text{ortho}} = \alpha\sigma_{\text{I}} + \beta\sigma_{\text{R}} + \phi v + h \quad (4)$$

where  $v$  is the steric substituent constant (Aslam *et al* 1981).

In order to identify and assess the relative importance of inductive, resonance and steric effects in ortho-substituted phenylmercaptoacetic acids, we have chosen two types of reactions where the reaction site i.e. sulphur atom is (i) in close proximity to the ortho-substituent, and (ii) is not close but away from the ortho-substituent. For the first type we have chosen the kinetics of bromamine T (BAT) and metaperiodate ( $\text{IO}_4^-$ ) oxidations of these acids, and for the second type the ionization constants of these acids. The kinetic data and the  $pK_a$  values have been correlated with various single- and multi-parameter equations.

## 2. Experimental

Phenylmercaptoacetic acid and ortho-substituted phenylmercaptoacetic acids were prepared by the reaction of chloroacetic acid and the corresponding thiophenol following the procedure for the preparation of *p*-substituted acids (Srinivasan and Pitchumani 1979). *o*-Nitrophenylmercaptoacetic acid was obtained by the reaction of *o*-chloronitrobenzene with thioglycolic acid (Glaasz 1912). The kinetic measurements were carried out under pseudo first-order conditions by estimating the unreacted oxidant using the iodometric procedure. Rates of BAT and  $\text{IO}_4^-$  oxidations were measured in 0.1 M aqueous potassium hydroxide and in 50% buffered  $\text{CH}_3\text{OH}-\text{H}_2\text{O}$  (v/v) respectively. The rate constants were determined at three temperatures. The rate data at 35°C for BAT and at 30°C for  $\text{IO}_4^-$  oxidations are taken as representative sets for the analysis of the ortho-effect. The  $pK_a$  measurements were made at 30°C in 50% aqueous ethanol (v/v) by careful partial neutralization of the acids with carbonate-free sodium hydroxide solution and taking about 20 pH readings between 10–15 and 60–70% neutralization. pH was measured with a digital pH meter, pH 5651 (ECIL). The  $pK_a$  values were calculated following the method of Pasto (Pasto and Kent 1965). Statistical calculations were carried out with an IBM 1130 computer.

## 3. Results and discussion

### 3.1 Rates of oxidation of ortho-substituted phenylmercaptoacetic acids by BAT and $\text{IO}_4^-$

It has been established that the oxidations of phenylmercaptoacetic acids is overall second-order, first order each in the substrate and the oxidant (Subramaniam 1987). Studies with *p*- and *m*-substituted acids show that the mechanisms in both oxidations involve the attack of the oxidant on the sulphur atom; the product is sulphinylacetic acid in each case (Subramaniam 1987). The second-order rate constants at three temperatures,  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  values and the ortho/para ratio of the rate constants are given in tables 1 and 2. It is clear from the data that all *o*-substituted acids react at a lower rate than the unsubstituted acid barring *o*-ethyl

**Table 1.** Second-order rate constants, enthalpies and entropies of activation for the oxidation of *o*-substituted phenylmercaptoacetates by BAT.

Substi- tuent	$10^3 k_2^a$ ( $M^{-1} s^{-1}$ )			$\Delta H^{\ddagger b}$ ( $kJ mol^{-1}$ )	$-\Delta S^{\ddagger b}$ ( $J K^{-1} mol^{-1}$ )	$k_{ortho}$
	35°C	45°C	55°C			$k_{para}$ at 35°C
H	65.3 ± 6.2	165 ± 4.8	408 ± 20	74.1 ± 6.7	27.6 ± 24	1.00
CH <sub>3</sub>	63.7 ± 1.7	145 ± 5.2	304 ± 11	63.0 ± 2.8	63.5 ± 9.4	0.388
C <sub>2</sub> H <sub>5</sub>	59.9 ± 1.4	135 ± 2.9	264 ± 9.7	59.7 ± 2.3	74.7 ± 7.7	0.392
OC <sub>2</sub> H <sub>5</sub>	58.8 ± 1.7	125 ± 4.6	241 ± 9.4	56.6 ± 2.9	84.9 ± 9.7	—
OCH <sub>3</sub>	55.9 ± 1.3	119 ± 3.7	225 ± 6.2	55.9 ± 2.3	87.7 ± 7.7	0.203
Br	6.25 ± 0.21	14.7 ± 1.2	30.1 ± 3.7	63.4 ± 6.7	81.4 ± 22	0.563
I	5.15 ± 0.28	11.6 ± 0.88	20.3 ± 1.7	55.1 ± 6.0	110 ± 20	0.267
Cl	1.95 ± 0.08	4.19 ± 0.21	9.42 ± 0.62	63.5 ± 4.4	91.2 ± 15	0.104
F	1.23 ± 0.12	2.65 ± 0.09	6.62 ± 0.51	68.0 ± 5.9	80.6 ± 20	0.030
NO <sub>2</sub>	47.4 ± 3.5	138 ± 7.3	(15.8 ± 1.2) <sup>c</sup>	82.9 ± 5.7	1.51 ± 20	46.9

General conditions: [PMA] = 0.0075 M; [BAT] = 0.00075 M; [KOH] = 0.1 M;

<sup>a</sup>The error quoted in  $k_2$  is 95% CL of the Student's  $t$ ;

<sup>b</sup>The precision of  $\Delta H^{\ddagger}$  and  $\Delta S^{\ddagger}$  values were calculated using the method of Petersen *et al* (1961);

<sup>c</sup>Rate constant at 25°C.

**Table 2.** Second-order rate constants, enthalpies and entropies of activation for the oxidation of *o*-substituted phenylmercaptoacetic acids by metaperiodate.

Substi- tuent	$10^2 k_2^a$ ( $M^{-1} s^{-1}$ )			$\Delta H^{\ddagger c}$ ( $kJ mol^{-1}$ )	$-\Delta S^{\ddagger c}$ ( $J K^{-1} mol^{-1}$ )	$k_{ortho}$
	20°C	30°C <sup>b</sup>	40°C			$k_{para}$ at 30°C
H	2.13 ± 0.02	3.89 ± 0.12	7.48 ± 0.13	45.4 ± 1.4	122 ± 4.9	1.00
CH <sub>3</sub>	2.21 ± 0.03	4.11 ± 0.12	7.58 ± 0.21	44.5 ± 1.8	125 ± 6.3	0.620
C <sub>2</sub> H <sub>5</sub>	2.52 ± 0.04	4.35 ± 0.18	7.97 ± 0.18	41.4 ± 2.0	134 ± 7.0	0.718
OC <sub>2</sub> H <sub>5</sub>	1.66 ± 0.02	2.98 ± 0.07	5.50 ± 0.06	43.2 ± 1.2	132 ± 4.2	—
OCH <sub>3</sub>	1.51 ± 0.03	2.85 ± 0.06	4.85 ± 0.06	42.0 ± 1.4	136 ± 4.9	0.357
Br	0.590 ± 0.03	1.06 ± 0.03	2.11 ± 0.07	46.0 ± 2.8	131 ± 9.9	0.442
I	0.544 ± 0.01	1.06 ± 0.02	1.98 ± 0.10	46.8 ± 2.2	129 ± 7.7	—
Cl	0.499 ± 0.01	0.869 ± 0.03	1.90 ± 0.06	48.4 ± 2.2	124 ± 7.7	0.343
F	0.426 ± 0.01	0.823 ± 0.02	1.62 ± 0.06	48.4 ± 2.1	125 ± 7.4	0.232
NO <sub>2</sub>	0.116 ± 0.003	0.265 ± 0.01	0.620 ± 0.02	61.4 ± 2.4	91.7 ± 8.5	0.548

General conditions: [PMAA] = 0.01 M; [NaIO<sub>4</sub>] = 0.00075 M; pH = 5.93; solvent: 50% methanol-50% water (v/v)

<sup>a</sup>The error quoted in  $k_2$  is 95% CL of the Student's  $t$ ;

<sup>b</sup>Average of the rate constants at three different concentrations.

<sup>c</sup>The precision of  $\Delta H^{\ddagger}$  and  $\Delta S^{\ddagger}$  values were calculated using the method of Petersen *et al* (1961).

and *o*-methyl compounds in IO<sub>4</sub><sup>-</sup> oxidation. The ratio  $k_{ortho}/k_{para}$  reflects considerable rate retardation by *o*-substituents in both oxidations. The order of reactivity in the BAT oxidation is H > Me > Et > OEt > OMe ≫ Br > I > Cl > F whereas in the IO<sub>4</sub><sup>-</sup> oxidation it is Et > Me > H > OEt > OMe > Br ≈ I > Cl > F > NO<sub>2</sub>. However, the rate of BAT oxidation of *o*-nitrophenylmercaptoacetic acid is very high and the cause is not clear. Therefore, this acid is not included in the correlation analysis of BAT oxidation.

The applicability of Taft's linear free energy-polar energy relationship, (1), and the linear free energy-steric energy relationship (2), has been tested with the rate data and the results are expressed in the following equations.

## BAT oxidation

$$\begin{aligned}\log k_{\text{ortho}} &= -2.73 \sigma_0^* - 1.58, \\ r &= 0.920; s = 0.315; n = 7,\end{aligned}\quad (5)$$

( $r$  = correlation coefficient;  $s$  = standard deviation;  $n$  = number of data points).

$$\begin{aligned}\log k_{\text{ortho}} &= 0.647 E_s - 2.19, \\ r &= 0.411; s = 0.735; n = 7,\end{aligned}\quad (6)$$

IO<sub>4</sub><sup>-</sup> oxidation

$$\begin{aligned}\log k_{\text{ortho}} &= -0.956 \sigma_0^* - 1.64, \\ r &= 0.956; s = 0.123; n = 8.\end{aligned}\quad (7)$$

$$\begin{aligned}\log k_{\text{ortho}} &= 0.460 E_s - 1.98, \\ r &= 0.684; s = 0.306; n = 8.\end{aligned}\quad (8)$$

The values of  $\sigma_0^*$  and  $E_s$  were those given by Taft (1956). The results of the analyses (see correlation coefficients) show that the observed reactivity of *o*-substituted phenylmercaptoacetic acids with BAT or IO<sub>4</sub><sup>-</sup> is not compatible with either the size of the substituents or with Taft's polar substituent parameter.

The ratio of the rate constants,  $k_{\text{ortho}}/k_{\text{para}}$ , is frequently considered as a measure of the steric effect of the *o*-substituent (Taft *et al* 1950). For both oxidations poor correlations are obtained between  $\log k_{\text{ortho}}/k_{\text{para}}$  and  $E_s$ , (9) and (10), indicating the minor role of the 'primary steric effect' or the 'bulk effect'.

## BAT oxidation

$$\begin{aligned}\log k_{\text{ortho}}/k_{\text{para}} &= 0.310 E_s - 0.211; \\ r &= 0.469; s = 0.192; n = 6.\end{aligned}\quad (9)$$

IO<sub>4</sub><sup>-</sup> oxidation

$$\begin{aligned}\log k_{\text{ortho}}/k_{\text{para}} &= 0.448 E_s - 0.160, \\ r &= 0.647; s = 0.120; n = 6.\end{aligned}\quad (10)$$

Thus the single-parameter equations do not yield satisfactory correlations confirming the recent view (Gallo 1983) that any single-parameter scale defined by any method, experimental, geometrical, physical or theoretical, is unlikely to be of general use for the treatment of the steric effect. Therefore, the rate data were analysed by Charton's method using (3) and (4). The literature values of  $\sigma_I$ ,  $\sigma_R$  and  $\nu$  (Aslam *et al* 1981) are employed. The multiple regression analyses of the rate constants yield the following results for the BAT oxidation,

$$\log k_{\text{ortho}} = -3.46 \sigma_I - 1.52 \sigma_R - 1.30, \quad (11)$$

$$(\pm 0.537) \quad (\pm 0.571)$$

$$R = 0.935; SE = 0.295; n = 9; CL = 99.5\%,$$

( $R$  = multiple correlation coefficient;  $SE$  = standard error of the estimate;  $n$  = number of data points;  $CL$  = confidence level of  $F$ -test significance).

$$\log k_{\text{ortho}} = -3.56 \sigma_1 - 1.58 \sigma_R + 0.252 v - 1.41, \\ (\pm 0.614) (\pm 0.623) (\pm 0.521) \quad (12)$$

$$R = 0.938; SE = 0.316; n = 9; CL = 99\%.$$

Similar analyses with the rate data for the the  $\text{IO}_4^-$  oxidation give the following equations,

$$\log k_{\text{ortho}} = -1.59 \sigma_1 - 0.593 \sigma_R - 1.45, \\ (\pm 0.063) (\pm 0.066) \quad (13)$$

$$R = 0.995; SE = 0.046; n = 10; CL > 99.9\%,$$

$$\log k_{\text{ortho}} = -1.58 \sigma_1 - 0.587 \sigma_R - 0.007 v - 1.44 \\ (\pm 0.092) (\pm 0.088) (\pm 0.068) \quad (14)$$

$$R = 0.994; SE = 0.050; n = 10; CL > 99.9\%,$$

The results of the multiple regression analyses reveal that in both oxidations the correlation is good when (3) is employed. This is judged from the high confidence level, low standard error and high correlation coefficient of the regression analysis [see (11) and (13)].

The insignificant role of the steric term is seen from the fact that the standard errors for the coefficient  $\phi$  are large in both oxidations [see (12) and (14)] and also the confidence levels for the significance of  $\phi$  term are less than 50% of the Student's *t*-test.

The significance of (11) and (13) have been tested by means of *F*- and *t*-tests. The confidence level *F*-test significance both for BAT and  $\text{IO}_4^-$  oxidations are greater than 99.5%. The confidence levels of the *t*-test for  $\alpha$  and  $\beta$  are above 99.9% except for  $\beta$  in (11) where it is 95%. The regression coefficients of  $\sigma_1$  and  $\sigma_R$  are all negative indicating that electron-releasing groups accelerate the rate and electron-withdrawing groups retard it as determined for *m*- and *p*-substituted phenylmercaptoacetic acids (Subramaniam 1987). Further, it is clear from the magnitude of the susceptibility constants that the effect of substituents is mainly controlled by the localized (inductive) effect. The order of reactivity in the BAT oxidation resembles that of the oxidation of *o*-substituted phenyl methyl sulphides by various oxidants (Srinivasan *et al* 1984). These sulphides react at a lower rate than the parent and this behaviour has been explained on the basis of electrical effects. In the  $\text{IO}_4^-$  oxidation *o*-ethyl and *o*-methyl compounds have a slightly higher rate as compared to the parent. The fairly large inductive effect in  $\text{IO}_4^-$  oxidation ( $\rho_1/\rho_R = 2.69$  for  $\text{IO}_4^-$  and 2.25 for BAT oxidations) and the negative  $\sigma_1$  for *o*-ethyl and *o*-methyl groups probably lead to a slightly higher rate constant than the parent. It may, therefore, be concluded that in both oxidations\* the electrical effects alone are sufficient to account for the *o*-substituent effect and the steric effect is insignificant.

### 3.2 Isokinetic relationships

Excellent Exner plots (plot of  $\log k_{55^\circ}$  vs.  $\log k_{35^\circ}$  for BAT oxidation and plot of  $\log k_{40^\circ}$  vs.  $\log k_{20^\circ}$  for  $\text{IO}_4^-$  oxidation) are obtained for both oxidations ( $r > 0.995$ )

\*The results of the complete statistical analyses at three temperatures are available with the authors.

and this is an indication of the operation of the same mechanism in all the substrates in each reaction series.

### 3.3 Quantitative treatment of the ionization constants of *o*-substituted phenylmercaptoacetic acids

When the reacting group (the carboxyl group) is not close to the *o*-substituent it will be of interest to examine how the ionization constants are influenced by the substituents in *o*-substituted phenylmercaptoacetic acids. Therefore, in the present study the  $pK_a$  values of ten *o*-substituted phenylmercaptoacetic acids have been determined in 50% aqueous ethanol (v/v) at 30°C (table 3). The  $pK_a$  values decrease in the order OEt > OMe > Et > Me > H > F > Cl > I = Br > NO<sub>2</sub> for the *o*-substituted acids. Treatment of the  $pK_a$  values by Taft's equations (1) and (2) results in the following expressions.

$$pK_a = -0.471 \sigma_0^* + 4.79, \\ r = 0.979; s = 0.042; n = 8, \quad (15)$$

$$pK_a = +0.290 E_s + 4.61, \\ r = 0.896; s = 0.089; n = 8, \quad (16)$$

A satisfactory correlation with  $\sigma_0^*$  implies that all effects other than polar are absent or are nearly constant as equivalent to the methyl group.

In *o*-substituted benzene derivatives where the substituent and reaction site are not adjacent or close, the rate or equilibrium data can be correlated by the simple Hammett equation using the  $\sigma_p$  constants on the assumption that electrical effects are about the same order of magnitude for *o*- and *p*-substituents (Charton 1960). The  $pK_a$  values give a good correlation with  $\sigma_p$ , (17), confirming the absence of any primary steric effect.

$$pK_a = -0.541 \sigma_p + 4.73, \\ r = 0.993; s = 0.022; n = 10. \quad (17)$$

A quantitative picture regarding the operation of inductive, resonance and steric effects (if any) can be gained by analysing the  $pK_a$  values using Charton's equations (3) and (4); the results are given below.

$$pK_a = -0.553 \sigma_I - 0.518 \sigma_R + 4.73, \\ (\pm 0.026) (\pm 0.027) \quad (18)$$

$$R = 0.997; SE = 0.019; n = 10; CL > 99.9\%,$$

$$pK_a = -0.554 \sigma_I - 0.519 \sigma_R + 0.001 v + 4.73, \\ (\pm 0.037) (\pm 0.036) (\pm 0.028) \quad (19)$$

$$R = 0.995; SE = 0.020; n = 10; CL > 99.9\%.$$

In the above treatment the *o*-nitro group has been assumed to be coplanar. (The correlation is not improved when *o*-nitro group is assumed to be orthogonal.) It is

**Table 3.**  $pK_a$  values of *o*-substituted phenylmercaptoacetic acids in 50% aqueous ethanol (v/v).

Substituent	OC <sub>2</sub> H <sub>5</sub>	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	H	F	Cl	I	Br	NO <sub>2</sub>
$pK_a$	4.89	4.87	4.83	4.79	4.74	4.68	4.60	4.58	4.58	4.32

clear from the results of the regression analyses that the steric effect is completely absent as shown by the high standard error and also by the low *t*-test significance of the term  $\phi$  (< 50%) in (19). Consequently the  $pK_a$  values are controlled by the electrical effects [results in (18)]. This is substantiated by the high multiple correlation coefficient, low standard error of the estimate, and by the 99.9% confidence levels for the significance (*F*-test), as well as by the 99.9% confidence levels for the significance of the terms  $\alpha$  and  $\beta$  by means of Student's *t*-test for (18). From the magnitudes of  $\alpha$  and  $\beta$ , it is evident that the inductive effect is slightly predominant over the resonance effect. The negative signs of the coefficients indicate that electron-releasing groups increase the  $pK_a$  values.

#### 4. Conclusion

It may be concluded that electrical effects alone are sufficient to account for the effect of the *o*-substituent on the rate (oxidation rates) and equilibrium data (ionization constants) of *o*-substituted phenylmercaptoacetic acids. Thus in these acids, whether the reaction site is in close proximity to the *o*-substituent or not, the steric effect is insignificant. BAT and IO<sub>4</sub><sup>-</sup> oxidations of *o*-substituted phenylmercaptoacetic acids are mainly controlled by the localized effect and not by the delocalized effect. The ionization constants of these acids are also determined by the inductive effect.

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