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Ortho-Substituent Effects on Reactivities of Benzohydroxamic Acids

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ORTHO-SUBSTITUENT EFFECTS
ON REACTIVITIES
OF BENZOHYDROXAMIC ACIDS

by

Irl E. Ward

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment
of the
Degree of Master of Arts

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Irl Eugene Ward

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HISTORY AND PURPOSE

Many empirical relations involving reactivities of organic compounds have been shown to be linear involving logarithms of rate or equilibrium constants. At constant temperature, the logarithm of a rate constant for a reaction is linearly related to the standard free energy of activation (ΔG^\ddagger) while for a reaction the logarithm of the equilibrium constant, K , is proportional to the standard free energy of reaction (ΔG°).¹

In the 1930's "linear free energy relationships" were studied by Hammett² for a number of systems involving side chain reactions of benzene systems. Specifically, Hammett studied substituent effects using the ionization of substituted benzoic acids as his standard system. His work led to the formulation of the "Hammett equation" which describes meta- and para-substituent effects on side chain reactions of benzene derivatives and is quantitatively given as:

$$\text{or} \quad \log (k/k_o) = \sigma \rho \quad (1)$$

$$\log (K/K_o) = \sigma \rho \quad (2)$$

k or K represent the rate constant or equilibrium constant, respectively, of the reaction involving the meta- or para-substituted benzene derivative, and k_o or K_o rep-

represent the rate constant or equilibrium constant, respectively, of the reaction involving the parent system. The polar constant, σ , represents the polar effect of the substituent on the reaction relative to hydrogen and is, by nature, independent of the reaction type. The reaction constant, ρ , measures the susceptibility of the reaction to polar effects and is, by nature of the linear free energy relation, a constant for all substituents and depends only on the reaction series, temperature and solvent.

For the ionization of substituted benzoic acids at 25°C, Hammett defined $\rho = 1.000$ and then used the relation,

$$\log (k/k_o) = \sigma \rho$$

to calculate values of σ for many substituents. The equation was found to be applicable to all but a few members of a series of fifty-two reactions. The definition of $\rho = 1.000$ for the benzoic acid reaction is a purely arbitrary selection¹ and is defined as such for the ionization of benzoic acid because of the linear relation between log of k for this "standard" reaction and log of k or K for so many other reactions.

The Hammett equation was applied to a series of 351 reactions by Jaffe' in 1953^{3,4} and was found to describe reactivities in all but a few reactions. By this time, however, a significant number of exceptions had been recorded contradicting the uniqueness property of the

substituent constant, σ . One example was most evident. The ionization of para-nitrobenzoic acid gave a value of $\sigma = 0.778$ for the para-nitro group. However, this value of σ proved inapplicable when applied to other reactions, such as reactions of anilines or phenols, where a value of $\sigma = 1.27$ was required for the para-nitro group.² This dual value of σ observed for the para-nitro substituent was observed with other substituents as well when applied to reactions of anilines and phenols. The increased value for σ_{NO_2} was attributed to cross-conjugation of the para-nitro substituent with the O^- in phenol anions or the $:\text{NH}_2$ in anilines which could not be explained in Hammett's equation by a simple polar substituent constant (σ). These "duality of substituent constants" were observed further in the reaction series examined by Jaffe'.

The concept of "duality" was extensively criticized by Wepster in the 1950's.⁵ Wepster viewed this high value for σ as a result of not only resonance interaction of the para-substituent with the aromatic ring, but also as resonance interaction of the reaction center with the para-substituent through the ring. Thus, a multiple number of values or a "sliding-scale" of values for σ should be expected rather than one value for "normal" reaction series and a single high value for "abnormal" reaction series.²

This resonance contribution to the polar constant is most pronounced in electron withdrawing substituents.

In fact, with the substituents in the ortho-position, steric effects become significant to the point of the failure of the Hammett equation.⁴ The failure of the Hammett equation for ortho substituents was studied by Kindler.^{4,6} He first observed a relationship between the basic hydrolysis of ethyl meta- and para-substituted cinnamates and the corresponding rates of ethyl meta- and para-benzoates. The failure of ortho-substituents to obey the relation was attributed to a steric "ortho effect" for the benzoate system.

Later, Ingold devised a more general method for separation of polar and steric effects in ester hydrolysis.⁴ According to this proposal, the ratio of the rate constants of alkaline to acidic hydrolysis is a function of the polarity of the substituent, even though both show steric effects.

Following this line, Taft proposed the following equation describing the polar effect of a substituent R as illustrated in the hydrolysis of the ester R-COO-R':⁴

$$\sigma^* = \left[(\log k/k_o)_{\text{B}} - (\log k/k_o)_{\text{A}} \right] / 2.48 \quad (3)$$

σ^* represents the polar effect of a substituent as measured from ester hydrolysis and is a purely polar effect;

k represents the rate constant for hydrolysis of the substituted ester, $R\text{-COO-R'}$, while k_0 is the rate constant for hydrolysis of the parent ester, Me-COO-R' . B and A refer to the basic or acidic catalyzed hydrolysis. The factor 2.48 is an arbitrary constant introduced so the values of σ^* will be put approximately the same scale as the Hammett σ values. The terms on the right side of the equation have the following significance: $(\log k/k_0)_B$ represents the sum of polar, steric, and resonance effects of R; $(\log k/k_0)_A$ represents the sum of steric and resonance effects of R, the difference giving the purely polar effect of R. The steric effect of R can thus be suitably represented by the equation:

$$E_s = (\log k/k_0)_A \quad (4)$$

although for both aliphatic and aromatic systems in which R contains a π -system conjugated with the ester function there is a resonance contribution to E_s .

The resonance contribution to substituent effects has been studied in terms of polar parameters.² The inductive contribution to the substituent effect, σ_I , is based on aliphatic and acyclic reactivities and is reaction independent. The resonance contribution, σ_R , was shown to be reaction-dependent, but an unenhanced resonance parameter, σ_R^0 , was defined, in terms of an "insulated reaction series," as the resonance contribution, when the reaction

center was not conjugated with the ring, which results in no direct resonance between the reaction center and the ring. The values of σ_I , and σ_R^0 were thus appropriately combined to yield the normal substituent constant σ^0 .

Taft's procedure is based on three assumptions:⁴

1. The relative free energy of activation can be treated as a sum of independent contributions from polar, steric and resonance effects.
2. In corresponding acidic and basic catalyzed hydrolyses the steric and resonance effects are cancelled in the difference:

$$(\log k/k_0)_B - (\log k/k_0)_A$$

3. The polar effects of substituents are much greater in basic than in acidic catalyzed ester hydrolysis.

If assumption (1) were invalid, Taft's entire argument would be vounded, for it is on this principle that separation analysis is feasible. Support for this assumption is provided by the usefulness and validity of results obtained in applying it. Justification of assumption (2) lies in the similarity of transition states of both acidic and basic catalyzed hydrolysis of esters. Recorded values of ρ supply evidence for assumption (3). Since for basic ester hydrolysis, ρ commonly lies within the range +2.2 to +2.8 and for acidic ester hydrolysis between -0.2 to +0.5, the polar effect is observed to be much greater in the basic reactions.

Since, in acidic hydrolysis of esters, the polar effect

of substituents was found to be small, it was possible to relate a function of the rate constants to steric effects. Taft found that a number of reactions conformed to the equation:

$$\log (k/k_o) = \delta E_s \quad (5)$$

where δ represents the steric susceptibility constant. For example, the acidic hydrolysis of ortho-substituted benzamides conforms to this equation which indicates, for this reaction series, that the polar effects of the ortho-substituents are zero or nearly so. Further examples of the applicability of this equation are very limited since polar effects must be minimal in reactions correlated by this relation.

However, wider applicability may be obtained from the summation of the steric contribution above and the polar contribution previously described into a final equation proposed by Taft and Pavelich:⁷

$$\log (k/k_o) = \sigma^* \rho^* + \delta E_s \quad (6)$$

This equation assumes the validity of assumption (1) previously introduced. The applicability of this equation has been extended over the range of basic and acidic catalyzed ester hydrolysis and has been applied to the

hydrolysis of aromatic and aliphatic amides and in modified form, to basic hydrolysis of anilides, and to reaction systems quite different from those defining σ^* and E_s .⁸ However, the validity of application may only be determined through experimental results. It is these results which either support or invalidate the assumption that the free energy of activation, and thus log of the rate constant, can be expressed as a sum of independent polar, steric and resonance contributions. Validity of this assumption is the heart of the Taft-Pavelich equation. Herein lies one of the purposes of this research. σ^* values are independent of reaction type and applicability of the Taft-Pavelich relation to other systems utilizing substituents with recorded σ^* values provides additional evidence for the validity of the Taft assumption mentioned. Valid application of the Taft relation also provides information related to the reaction steps within the reaction mechanism.

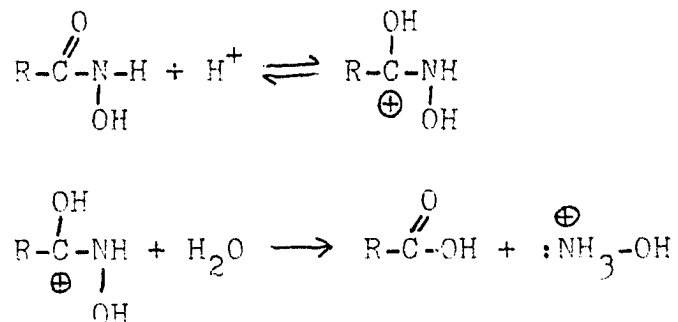
Finally, the Taft relation has been applied to a considerable number of aliphatic and aromatic systems for which steric interaction has caused failure in the Hammett equation. However, relatively few ortho substituted aromatic systems have been studied. Application of the 2-parameter Taft equation to such selected systems provides a good opportunity to test the "independence of effects" assumption made by Taft. The proximity of groups in the

ortho position can easily present steric effects not found in other systems.

Studies of aliphatic hydroxamic acids have shown that their acidic hydrolysis rate constants are pseudo-first order under conditions of excess catalytic acid.⁹ Correlation of $\log k$ with only σ^* or E_s proved to be very poor. However, utilization of the 2-parameter relation provided a fairly good correlation. This result contrasts with that for the acidic hydrolysis of amides for which good correlation results between $\log k$ and E_s with little dependence on polar effects.^{2,4}

Extension of the two parameter relation to ortho substituted benzohydroxamic acids allows this comparison to be extended to an aromatic system in which, in the ortho position, steric effects should have a much greater influence than in the meta or para positions.

Indications are that since $\rho^* < 0$ in the acidic hydrolysis of aliphatic hydroxamic acids, the polar effects of the substituents in the nucleophilic attack by water on the protonated hydroxamic acid should not predominate in importance over the polar effects of the substituent in the protonation step within the mechanism.⁹ These two steps can be illustrated by the following accepted mechanism.^{9,10,11}



Lastly, it has been suggested that σ^* is not an actual measurement of polar substituent effects for alkyl substituents which have small σ^* values (0 to -0.3).⁸ Such small values of σ^* might arise from imperfect steric cancellation in the Taft analysis (assumption #2). This is explained by considering the uncertainty of the Taft expression. Ritchie claims that for reactions which obey the Taft equation

$$\log (k/k_o) = \rho^* \sigma^*$$

the value for σ^* for all alkyl substituents might as well be zero as be the value obtained from Taft's relation. He considers the σ^* values to arise from interaction of various types of substituent effects. In other words, that Taft's assumption of the free energy of activation being a summation of independent substituent effects is fallacious. By the use of alkyl substituents, and others, in various independent systems, valid confirmation to the Taft relation

not only strengthens the premise that σ^* values used are a valid indication of the polar effect of substituents, but also that Taft's free energy assumption is a correct one applicable to a wide variety of reaction systems. In addition, further light is automatically shed on the effects of ortho substituents on hydroxamic acid reactivities.

EXPERIMENTAL METHOD, APPARATUS AND SYNTHESSES

Preparation of Ortho-Substituted Methyl Benzoates

The preparation of the above mentioned benzoates for use in the preparation of ortho-substituted benzohydroxamic acids followed a general procedure illustrated by the preparation of methyl ortho-bromobenzoate.¹⁰ The following procedure is, therefore, applicable to the preparations of all esters: methyl ortho-ethoxybenzoate, methyl ortho-methoxybenzoate, methyl ortho-bromobenzoate and methyl ortho-nitrobenzoate.

Ortho-bromobenzoic acid (25 grams) was refluxed with 100 ml. of A.C.S. grade methanol and 5.0 ml. concentrated sulfuric acid (97%) for seventy-two hours. The resulting solution was quenched with solid sodium carbonate and made basic (pH 10) with aqueous sodium hydroxide (~2M). The crude methyl ester was extracted with diethyl ether in three 50 ml. portions. The ether solution was dried with magnesium sulfate and the excess solvent air evaporated yielding the liquid yellow ester. The yield was 21.6 grams (~83%). The following table illustrates the product yields for each ester obtained.

TABLE I
YIELDS OF PREPARED ESTERS

Compound	Yield, grams ^a
Methyl <u>ortho</u> -bromobenzoate	21.6
Methyl <u>ortho</u> -methoxybenzoate	18.9
Methyl <u>ortho</u> -ethoxybenzoate	19.4
Methyl <u>ortho</u> -nitrobenzoate	23.2

^aYields are based on 25 g. of the corresponding acid.

Preparation of Methanolic Hydroxylamine

Hydroxylamine hydrochloride (46.7 g) was dissolved in 240 ml. of methanol. Potassium hydroxide (56.1 g) was dissolved in 140 ml. of methanol. Both were dissolved at the boiling point of the solvent. The potassium hydroxide solution was added to the hydroxylamine hydrochloride solution at approximately 60°C. The mixture was cooled overnight to complete precipitation of potassium chloride. The mixture was then filtered to separate the solid potassium chloride from the methanolic hydroxylamine solution.

Preparation of Ortho-Bromobenzohydroxamic Acid

Methyl ortho-bromobenzoate (21.6 g) was added to the hydroxylamine solution described above. The solution was filtered and let stand for seventy-two hours to complete reaction. The solution was then buffered to a pH~6 with

1.25N acetic acid and the excess solvent air evaporated to approximately 20-25 ml. The crude crystals were filtered and weighed. Some of the crystals were then dissolved in 175 ml. of 1.25N acetic acid, and the solution was allowed to stand twenty-four hours. Those crystals which did not dissolve were removed by filtration and allowed to dry overnight. They were weighed and the ferric chloride test was applied to a small amount of the crystals (~ 0.05 g). (For explanation of the ferric chloride test, see "Preparation of Reaction Solution and Kinetics Procedure.") The ferric chloride test was strongly positive; the crystals were dissolved in hot ethyl acetate, the solution was cooled and the resulting crystals were removed by filtration. They were washed with benzene and dried in air to yield 11.5 g, mp $148-150^{\circ}\text{C}$. The product was recrystallized twice from hot 3:7 (v/v) ethanol:water. The process gave 7.5 g of the hydroxamic acid, mp $177-178^{\circ}\text{C}$, lit.¹² $178-180^{\circ}\text{C}$.

Preparation of Ortho-Nitrobenzohydroxamic Acid

Methyl ortho-nitrobenzoate (10.0 g) was added to 100 ml. of the above mentioned hydroxylamine solution with shaking. The solution was warmed for twenty minutes at about 50°C and then allowed to stand at room temperature overnight. A small amount of crystals (~ 0.3 g) was formed and the crystals were collected. This substance exhibited

a weakly positive ferric chloride test. The reaction solution was then buffered to $\text{pH} \sim 6$ with 1.25N acetic acid and air evaporated to a dark orange oil (~ 30 ml.). The oil gave an intense positive ferric chloride test. The oil was dissolved in 20 ml. of 2-butanone and 4 ml. portions of concentrated hydrochloric acid (37.1%) were added, followed by filtration after each addition. The additions were continued until there was no resulting precipitation from the 2-butanone solution. The collective precipitate was dried and showed a negative ferric chloride test.

The slightly acidic mother liquor was air evaporated to about 10 ml. and cooled at -10°C for twenty-four hours to yield prism-like yellow crystals. The crystals were collected and gave an intensely positive ferric chloride test. They were recrystallized three times from ethyl acetate, dried and weighed to yield 1.35 grams of the ortho-nitrobenzohydroxamic acid melting at $131.5\text{--}132.5^{\circ}\text{C}$. Purity analysis of this compound is found in Tables II and IV.

Preparation of Ortho-Methoxybenzohydroxamic Acid

Methyl ortho-methoxybenzoate (18.9 g) was added with shaking to 200 ml. of the above mentioned hydroxylamine solution and allowed to stand for twenty-four hours. The resulting solution was then buffered to $\text{pH} \sim 6$ with acetic acid and then evaporated by an air stream to yield crude

crystals in an oily mother liquor. The crystals gave a positive ferric chloride test. The crude product was recrystallized three times from ethyl acetate and once from 3:7 (v/v) ethanol:water. The yield was 0.85 g, mp 124-126°C.

Preparation of Ortho-Ethoxybenzohydroxamic Acid

Methyl ortho-ethoxybenzoate (19.4 g) was added to 200 ml. of the above hydroxylamine solution with shaking and allowed to stand for seventy-two hours. The resulting solution was buffered with acetic acid and evaporated in an air stream until crystals just began to form. The solution was then placed in a freezer for one hour to yield crystals which gave an intense positive ferric chloride test. The crystals were recrystallized three times from 3:7 (v/v) ethanol:water. The yield was 2.19 g, mp 124-125.5°C.

Each of the above listed esters and new hydroxamic acids were structurally analyzed by infrared spectroscopy. The hydroxamic acids were also analyzed for percent carbon, nitrogen and hydrogen by Galbraith Labs., Inc., Knoxville, Tennessee. The following tables list these analyses.

TABLE II
ELEMENTAL ANALYSIS OF PREPARED HYDROXAMIC ACIDS

Compound	Analysis	% C	% N	% H
<u>Ortho</u> -nitrobenzo-hydroxamic acid	Theoretical	46.16	15.38	3.32
	Observed	46.10	15.32	3.36
<u>Ortho</u> -methoxybenzo-hydroxamic acid	Theoretical	57.48	8.38	5.43
	Observed	57.65	8.44	5.28
<u>Ortho</u> -ethoxybenzo-hydroxamic acid	Theoretical	59.65	7.73	6.13
	Observed	59.76	7.76	6.29

Infrared Analysis (Ester Preparations)

The characteristic ester peak observed at 1730-1715 cm^{-1} is represented by the corresponding carbonyl absorption.¹³ The following table illustrates the observed band for each ester prepared.

TABLE III
INFRARED ANALYSIS OF PREPARED ESTERS^a

Compound	Frequency of Carbonyl Absorption
Methyl <u>ortho</u> -bromobenzoate	1727 cm^{-1}
Methyl <u>ortho</u> -nitrobenzoate	1726 cm^{-1}
Methyl <u>ortho</u> -methoxybenzoate	1726 cm^{-1}
Methyl <u>ortho</u> -ethoxybenzoate	1724 cm^{-1}

^aEsters were all oils and samples were run as oils between salts.

Infrared Analysis (Hydroxamic Acid Preparations)

The characteristic hydroxamic acid peaks observed at 3300-3200 cm^{-1} and 1640-1620 cm^{-1} represent the N-H stretch absorption and carbonyl absorption respectively.¹³ The following table illustrates the observed bands for each of the new hydroxamic acids prepared.

TABLE IV
INFRARED ANALYSIS OF PREPARED HYDROXAMIC ACIDS^a

Compound	Carbonyl Absorption(cm^{-1})	N-H Absorption(cm^{-1})
<u>Ortho</u> -bromobenzo- hydroxamic acid	1620	3220
<u>Ortho</u> -nitrobenzo- hydroxamic acid	1625	3220
<u>Ortho</u> -methoxybenzo- hydroxamic acid	1625	3300
<u>Ortho</u> -ethoxybenzo- hydroxamic acid	1630	3250

^aAcids were powders and samples were run as Fluorolube mulls between salts.

Selection of Acid Solvent for Kinetics

For convenience, water was the first solvent tested. The water was doubly distilled and all of the prepared

hydroxamic acids, except ortho-nitrobenzohydroxamic acid, were tested for solubility at the 0.01M level and found to be soluble in hot water. Since water proved to be suitable, no other solvents were tested.

Preliminary kinetic runs at $90.00 \pm 0.05^{\circ}\text{C}$ using an acid concentration of 0.214M hydrochloric acid indicated the rates of hydrolyses of some of the hydroxamic acids would be too small for convenient measurement. An increase in the hydrochloric acid concentration to 0.60M was required. The new solution was standardized with a 0.574M sodium hydroxide solution which was standardized with a 0.250M potassium hydrogen phthalate solution. The following table illustrates the standardization results:

TABLE V
STANDARDIZATION OF ACID SOLVENT

Trial	ml NaOH used	HCl calculated
1	10.41	0.607 <u>M</u>
2	9.51	0.604 <u>M</u>
3	9.51	0.604 <u>M</u>
average HCl = 0.605 <u>M</u>		

Preparation of Standard Ferric Chloride Solution

Ferric chloride hexahydrate, 2 grams, was dissolved in 200 ml. of distilled water with 5-7 drops of concentrated hydrochloric acid (37%) added. The solution was

filtered and 10 ml. aliquots were pipetted into 25 ml. volumetric flasks. One flask was diluted to 25 ml. with distilled water and used as the blank solution. The others were used as sample flasks.

Preparation of Reaction Solution and Kinetics Procedure

The reaction solution was prepared in the following manner: a 0.01M solution of the prepared hydroxamic acid was made by dissolving the appropriate weight of acid into 15 ml. of 0.605M hydrochloric acid. Solution was accomplished by steam heating the outside of the 15 ml. reaction tube until all of the hydroxamic acid had dissolved. The solution was then placed in a constant temperature oil bath held at $90.00 \pm 0.05^{\circ}\text{C}$. The reaction solution was given typically five to ten minutes to come to temperature. At this point, a 1.00 ml. aliquot was pipetted into one of the previously prepared sample flasks containing the standard ferric chloride solution. The sample was then diluted to 25 ml. with distilled water, and the absorbance of the solution determined on the Beckman D. U. spectrophotometer using two 1-cm Beckman quartz cells at a wavelength setting of 520 nm. The absorbance was determined relative to the previously prepared blank solution.

The relative quantity of remaining unreacted hydroxamic acid is determined by the absorbance of the ferric

chloride-hydroxamic acid complex which forms in the sample flask. As the hydroxamic acid concentration decreases during hydrolysis, so does the concentration of the complex and thus the absorbance. The complex which forms is the characteristic purple magenta complex between ferric ion and the hydroxamic acid functional group.¹¹ At the complex concentration range under Beer's law has been shown to apply.⁹

The cells were calibrated by filling both with distilled water and measuring the absorbance of one relative to the other. The following illustrates the results:

<u>Sample Cell</u>	<u>Blank</u>	<u>% T</u>
A	B	99.8
B	A	100.3

Each 1.00 ml. sample aliquot was taken at a specified time interval depending on the speed of the reaction. The absorbance of each aliquot was taken for each sample run and the data plotted to obtain the observed rate constant. The following table illustrates the number of runs taken for each compound and the observed rate constant. For explanation of k_{obs} . derivation, see "Use of the D. U. Spectrometer."

TABLE VI

OBSERVED RATE CONSTANTS FOR HYDROLYSES OF HYDROXAMIC ACIDS

Compound	Trial	% Mean Deviation	Observed k (sec ⁻¹)
<u>Ortho</u> -methylbenzo-hydroxamic acid ^a	1		2.42 x 10 ⁻⁵
	2		2.59 x 10 ⁻⁵
	3		2.44 x 10 ⁻⁵
		3.95 Average	2.53 x 10 ⁻⁵
<u>Ortho</u> -methoxybenzo-hydroxamic acid	1		2.07 x 10 ⁻⁴
	2		2.20 x 10 ⁻⁴
	3		2.18 x 10 ⁻⁴
		2.57 Average	2.15 x 10 ⁻⁴
<u>Ortho</u> -ethoxybenzo-hydroxamic acid	1		1.62 x 10 ⁻⁴
	2		1.67 x 10 ⁻⁴
	3		1.64 x 10 ⁻⁴
		0.97 Average	1.64 x 10 ⁻⁴
<u>Ortho</u> -chlorobenzo-hydroxamic acid ^b	1		1.66 x 10 ⁻⁵
	2		1.98 x 10 ⁻⁵
	3		1.82 x 10 ⁻⁵
	4		1.82 x 10 ⁻⁵
		4.49 Average	1.82 x 10 ⁻⁵
<u>Ortho</u> -bromobenzo-hydroxamic acid	1		1.01 x 10 ⁻⁵
	2		9.75 x 10 ⁻⁶
	3		1.02 x 10 ⁻⁵
		1.80 Average	1.00 x 10 ⁻⁵

^{a, b} These acids were previously prepared by J. R. McDowell, mp 130.5-131°C and mp 159.5-160.1°C respectively.

The Constant Temperature Oil Bath

Reaction temperature was held constant at 90.00° ± 0.05°C by a constant temperature oil bath. The basic

apparatus employed is illustrated in Figure 1 on the following page.

The reaction cells were held at constant temperature by immersion into the constant temperature oil bath (A). A heating coil was connected to a voltage regulator to supply the necessary heating to keep the oil bath at constant temperature (B). A thermoregulator (C) was immersed to the same depth as the thermometer (D) which had been calibrated in 0.1°C increments, to ensure accurate temperature calibration. The thermoregulator was connected to the input terminals of a relay (E) which was, in turn, connected to the voltage regulator. The thermoregulator was then set at 90.00°C . To prevent extensive heat loss through the walls of the bath, the container was insulated with vermiculite packing. A mechanical stirrer (F) was also employed to ensure even heating throughout the bath. The apparatus, after being constructed, was tested for twenty-four hours to ensure precision in temperature control. Variation was never greater than $\pm 0.05^{\circ}\text{C}$.

Use of the Beckman D. U. Spectrometer

The D. U. Spectrometer was used to determine the absorbance of ferric ion-hydroxamic acid complex for each aliquot of the reaction solution. k_{obs} is calculated via the direct relationship between measured absorbance and hydroxamic acid concentration. The following derivation

illustrates this relationship between measured absorbance, $k_{\text{obs.}}$, and hydroxamic acid concentration.¹⁴ Since the hydrolysis rate is pseudo first order in hydroxamic acid,

$$\log \left(\frac{a}{a-x} \right) = \frac{kt}{2.303} \quad (7)$$

where a = initial amount hydroxamic acid,
 x = amount of acid reacted in time t , and
 k = first order rate constant.

Concentration of the hydroxamic acid may be related to some physical property, λ_t , which is directly proportional to concentration. For the above rate expression this may be illustrated as:

$$\log \left(\frac{a}{a-x} \right) = \log \left(\frac{\lambda_0 - \lambda_\infty}{\lambda_t - \lambda_\infty} \right) \quad (8)$$

where λ_∞ = measured property at time infinity, and
 λ_0 = measured property at time = 0.

Since absorbance is directly proportional to the concentration of hydroxamic acid, equation (8) may be written as:

$$\log \left(\frac{a}{a-x} \right) = \log \left(\frac{A_0 - A_\infty}{A_t - A_\infty} \right) \quad (9)$$

Since $A_\infty = 0$ for the hydroxamic acid-ferric ion complex, because at time infinity no hydroxamic acid remains, the rate expression is finally represented as:

$$\log A_t = \frac{-k_{\text{obs.}} \cdot t}{2.303} + \log A_0 \quad (10)$$

A plot of the log of measured absorbance ($\log A$) versus time (t) yields a slope of $-k_{\text{obs.}}/2.303$. Excellent psuedo-first-order plots were obtained in all cases.

Absorbances were determined at a fixed wavelength value which had been previously chosen based on the aliphatic hydroxamic acid series.⁹ A value of 520nm represents the wavelength maximum for the aliphatic series. Since the same type of complex forms in the aromatic series, the same wavelength value was used. The table illustrating values of $k_{\text{obs.}}$ for each compound and their percent deviations was presented above. From these values, application of the observed rate constant to the Taft-Pavelich equation was made. The next section gives a detailed discussion of this application.

RESULTS AND DISCUSSION

The values of ρ^* , δ and $\log k_0$ in equation (6) were determined by the method of least squares.¹⁵ Since the Taft-Pavelich equation is expressed as:

$$\log k = \rho^* \sigma^* + \delta E_s + \log k_0 \quad (6)$$

it may also be represented in a linear algebraic fashion as:

$$z = Bx + Cy + A \quad (11)$$

where: $z = \log k$

$$B = \rho^*$$

$$C = \delta$$

$$x = \sigma^*$$

$$y = E_s$$

$$A = \log k_0$$

Since E_s and σ^* are functions of the substituent and z was determined experimentally, a least squares treatment yielded calculated values for A , B and C and hence for $\log k_0$, ρ^* and δ . The following table lists values for σ^* , E_s and $\log k$ used in the least squares treatment. Solution of equation (11) using the least squares treatment yielded calculated values not only for ρ^* and δ , but also for $\log k_0$. From this determination, $\rho^* = -0.87$, $\delta = +0.76$ and

$\log k_o = -4.61$. These calculated values define the least squares fit of the data obtained for E_s , σ^* , and $\log k_i$, which is illustrated in Figure 2.

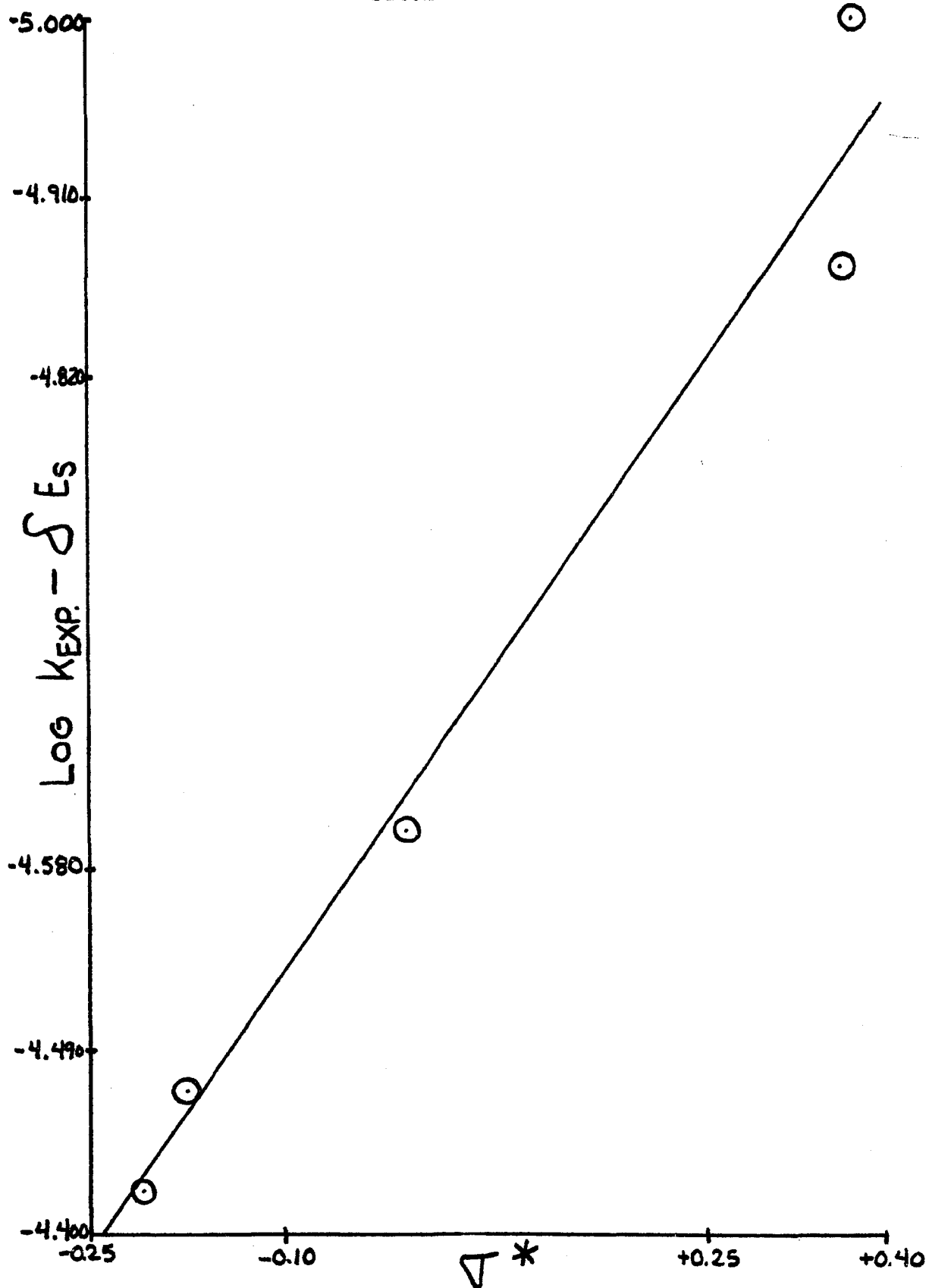
TABLE VII
ORTHO-SUBSTITUENT PARAMETERS USED IN THE
LEAST SQUARES MULTIPLE REGRESSION ANALYSIS

Ortho- Substituent	$\log k^b$ (exp.)	σ^{*a}	E_s^a	$\log k^b$ (calc.)
-CH ₃	-4.60	0	0	-4.61
-Cl	-4.74	+0.37	+0.18	-4.80
-Br	-5.00	+0.38	0	-4.94
-OCH ₃	-3.62	-0.22	+0.99	-3.67
-OC ₂ H ₅	-3.78	-0.18	+0.90	-3.77

^alit. values, Reference 8.
^b k , sec⁻¹

From Table VI, $\log k_o$ (experimental) = -4.60 which compares very favorably to the calculated value for $\log k_o = -4.61$. Determination of the standard deviations for the graphical representation of the least squares treatment of σ^* , $\log k_i - \delta E_s$ and $\log k_o$ (Figure 2) yielded values of 0.082, 0.048 and 0.022 respectively.

FIGURE 2



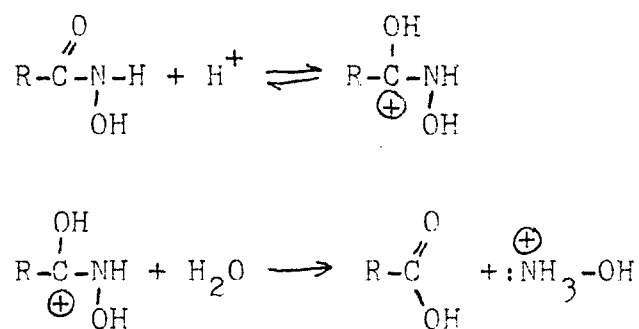
Since the experimental results give a straight line with relatively little scattering (Figure 2) calculated values for ρ^* , and δ , obtained from the least squares treatment, are representative values. The statistical significance of the observed data with the two parameter Taft-Favelich equation, as determined by least squares calculations was determined by the calculation of the coefficient of multiple regression (Correlation coefficient). This value is the square root of the ratio of the explained variation to the total variation of the experimental data. For the system studied, the correlation coefficient (R) was calculated to be 0.998. For a perfect correlation, $R = 1.000$. The value of 0.998 indicates near perfect correlation between observed data and the E_s and σ^* parameters.

The reliability of the correlation coefficient as a measure of statistical significance depends upon the number of data sets used in the least squares treatment and the number of variables calculated. The F-test¹⁵ allows for these factors and was applied to the calculated correlation coefficient. In this case, the number of data sets was five with three variables calculated. The F-test indicated the correlation to be within the 1% significance level, i.e., a very high level of significance

can be attributed to the correlation.

The calculated value of $\rho^* < 0$ is in agreement with that obtained for the aliphatic hydroxamic acid series previously studied.⁹ However, this ρ^* value is in contrast with the acid catalyzed hydrolyses of amides in both the aliphatic and ortho-substituted benzamide series, which show little or no dependence on polar effects.

The observed rate constants used in the calculation of ρ^* and δ are overall rate constants, i.e., a composite of two steps in the previously introduced accepted mechanism:^{9,10,11}



Buglass and coworkers¹⁶ have calculated rate constants for the second step for a series of para-substituted benzohydroxamic acids and report a positive Hammett ρ value for correlation of those rate constants. This value for ρ is consistent with the proposed bimolecular mechanism. Further examination of their data indicates fair correlation between their observed overall rate constants and Hammett σ values with the overall ρ value being negative. This

result, which is also consistent with the aliphatic hydroxamic acid series,⁹ is consistent with the ortho-substituted benzohydroxamic acid series where $\rho^* < 0$. From this result and the studies of Buglass and coworkers, the first step in the above mechanism is seen to be susceptible to polar effects to a much greater extent than is the second step. The reason for this greater susceptibility is seen when one considers a comparison of electronegativities between the hydroxamic acid hydroxyl group and the corresponding amide hydrogen. Displacement of electrons from the carbonyl center toward the electronegative hydroxyl group creates a partial positive charge on the carbonyl carbon. Addition of H^+ should, therefore, be more difficult in hydroxamic acids than protonation in amides without the effect of the electronegative hydroxyl group. With protonation more difficult, polar effects of ortho-substituents should be felt to a greater extent than they would be in amide protonation.

ρ was initially defined in terms of substituted benzoic acid ionization reactions and was assigned a value of 1.000 for this reaction in which electron withdrawing substituents augment the extent of ionization.¹ Therefore, for any reaction where electron withdrawing substituents accelerate the reaction, ρ will be positive. Conversely, where a reaction is accelerated by electron releasing substituents, ρ will be negative. Since for

the system studied in this research, ρ^* (overall) = -0.87 and for step (2) $\rho > 0$, it can easily be seen that the extent of the initial protonation of the ortho-substituted benzohydroxamic acid is increased by substituents which exhibit electron releasing effects.

The calculated value of $\delta = +0.76$ is consistent with the positive value obtained for the aliphatic hydroxamic acid series. A value of $\delta > 0$ would be predicted for large substituents in the ortho position since δ measures the susceptibility of the reaction system to steric effects. Since correlation with the two parameter Taft-Pavelich equation is excellent, the δ value obtained should be a representative value for the steric parameter.

δ was initially defined in terms of the acid hydrolyses of esters and assigned a value of 1.000 for that reaction. Therefore, for larger substituents which slow the reaction in proportion to their size, E_s becomes more negative with a positive value for δ . The magnitude of δ indicates whether susceptibility to steric effects of the reaction system being studied is greater or less than those in the reaction defining δ . The magnitude of steric effects within a reaction system is, therefore, a function of both the reaction's susceptibility to steric effects and substituent size. For acidic hydrolysis of ortho-substituted benzohydroxamic acids, the polar and

steric effects, relative to an ortho-methyl substituent, are given by $\rho^*\sigma^*$ and δE_s respectively. The polar effect is larger than the steric effect for the ortho-chloro- and ortho-bromo-substituents while the reverse is true for the ortho-alkoxy groups relative to the ortho-methyl substituent. This is illustrated in Table VIII.

TABLE VIII
OVERALL POLAR AND STERIC CONTRIBUTIONS
OF ORTHO-SUBSTITUENTS

<u>Ortho</u> -Substituent	δE_s	$\rho^*\sigma^*$	$\log k$, (calc.) ^a
-CH ₃	0	0	-4.61
-Cl	+0.14	-0.32	-4.80
-Br	0	-0.33	-4.94
-OCH ₃	+0.75	+0.19	-3.67
-OC ₂ H ₅	+0.68	+0.16	-3.77

^acalculated from equation (6).

The proximity of ortho-substituents in the system studied affords the possibility for the need of a corrected value for E_s due to possible interactions not accounted for in the simple two parameter Taft-Pavelich equation. Complications caused by substituent proximity is often referred to as the "Ortho-Effect".⁴ However, correlation with the simple Taft-Pavelich equation proved to be excellent ($R = 0.998$). Such satisfactory correlation sup-

plies further support for the "independence of effects" assumption made by Taft in his formulation of the simple two parameter equation.

Thus, in conclusion, this research extends the useful range of application of the Taft-Pavelich equation and supports that approach to understanding substituent effects on reactivity.

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VITA

The author was born in Rushville, Indiana on August 20, 1949. He graduated from Maine Township High School South in 1967 and entered Rose Polytechnic Institute that same year. He received his B. S. degree in chemistry in 1971 and entered Western Michigan University as a graduate student later that year. While completing the masters program in organic chemistry, the author was employed as a part time gas chromatographic technician and chemist at the A. M. Todd Company and is presently working in that capacity.

The author is married with no children.