Linear Free Energy Study of Ring-Substituted Aniline Ozonation for Developing Treatment of Aniline-Based Pesticide Wastes

Anthony C. Pierpoint,[†] Cathleen J. Hapeman,[‡] and Alba Torrents*,[†]

Environmental Engineering Program, Department of Civil and Environmental Engineering, University of Maryland, College Park, Maryland 20742, and Environmental Quality Laboratory, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland 20705

The relative rate constants for the reaction of ozone were determined for several substituted anilines in aqueous solutions at pH 6.5 and 1.5. At pH 6.5, with the exception of *m*- and *p*-nitroaniline, the rate constants obey Hammett's equation: $\log(k_X/k_H) = \rho\sigma$. The departure of *m*- and *p*-nitroaniline may be explained by direct conjugation of the reaction center. The commonly used σ_p^- value of 1.27, which extends the range of applicability of the Hammett equation, was insufficient to account for the conjugation effects on ozonation of *p*-nitroaniline; $\rho = -1.48$ ($R = 0.973$). Use of amine group atomic charge determinations significantly improved correlations: $(k_X/k_H) = 48.7\delta - 18.2$ ($R = 0.996$). A linear plot of Hammett constants versus relative rate data at pH 1.5 showed poor correlation: $\rho = 0.72$ ($R = 0.572$). Poor correlation was similarly observed for amine group atomic charge determinations, suggesting varied reaction mechanisms.

INTRODUCTION

Linear free energy relationships have long been used in physical organic chemistry to elucidate reaction mechanisms and estimate reactivities of compounds using known physical and chemical properties (*1−5*). Linear free energy relationships have also been used to study ozonation reactions for ring-substituted phenylethylenes (*6−9*). The reactions showed a Hammett dependence with an electrophilic mode of attack of ozone on the phenylethylenes. When these relationships exist, they can provide useful information to predict reaction rates and postulate plausible mechanisms. This study examines the effect of ring substituents on the ozonation of substituted anilines to further the development of treatment strategies for aniline-contaminated waste.

Anilines are present in a variety of industrial waste streams. They are widely used in the synthesis of dyes and, as such, they may be found in the waste streams of many textile plants. They are also used in the production of agrochemicals, pharmaceuticals, marking inks, photographic developers, resins, varnishes, and polishing agents (*10−12*). Many of the substituted anilines are resistant to biological degradation, therefore, other processes are required to detoxify the aniline-contaminated wastes (*13*). Aniline itself has been found to react rapidly with ozone; $k = (90 \pm 20) \times 10^6$ M^{-1} s^{-1} (*14*). However, the effects of ring substituents and pH on ozone reactions have not been fully examined.

Ozonation studies of several substituted anilines were carried out in aqueous solutions at pH 6.5 and 1.5. Relative rate values were then compared to Hammett constants and atomic charge determinations to establish whether these parameters can be used to (1) predict ozone reaction rates of the substituted anilines and (2) provide an indication of the effect of substituents on reaction mechanisms.

EXPERIMENTAL PROCEDURES

Materials. Stock solutions of aqueous ozone were prepared by passing a 0.5 L/min ozone/oxygen gas stream through a stirred reactor containing 0.5 L of pH-adjusted, distilled water. The gas stream ozone concentration was maintained at 2−6% and generated using a PCI ozone generator model GL-1B (PCI Ozone Corp., West Caldwell, NJ). Solutions comprised either a 50 mM phosphate buffer solution (pH 6.5) or distilled water adjusted to pH 1.5 with sulfuric acid. Aniline and the series of ortho-, meta-, and para-substituted anilines were of analytical grade (98% or greater) and were obtained from Sigma Chemical Co., J. T. Baker Chemical Co., Eastman Kodak Co., or Aldrich Chemical Co. *tert*-Butyl alcohol (99%) was obtained from Sigma Chemical Co. Analytical grade (99.5%) sodium nitrite, which was used to determine relative reaction rates for aniline and *m*-nitroaniline at pH 6.5, was obtained from Sigma Chemical Co., as were analytical grade (98%) cresol and phenol, which were used for relative rate determinations at low pH.

Ozonation. Contaminant ozonation rate constants were determined either by direct measurement or by the relative rate method. For direct measurements, ~20 mg of the target compound was dissolved in 10 mL of methanol, of which 100 μL was added to rapidly mixed 125 mL flasks containing 40−50 mL of either phosphate-buffered (pH 6.5) 10 mM *tert*-butyl alcohol or distilled water previously adjusted to pH 1.5 with concentrated sulfuric acid. *tert*-Butyl alcohol was added to scavenge hydroxyl radicals (*15*). Aqueous ozone was then added in 5-fold excess to the flask. At regular time intervals, a fixed amount of ozone/organic reaction mixture was pipetted into vials containing enough sodium hydrosulfide to quench the reaction. Alternatively, sodium hydrosulfide was added directly to reaction flasks at various time intervals. Rate constants were determined by eqs 1 and 2

$$\ln([M]_0/[M]_t) = k_{exp}t \tag{1}$$

* Author to whom correspondence should be addressed [e-mail alba@eng.umd.edu; fax (301) 405-2585].

[†] University of Maryland.

[‡] U.S. Department of Agriculture.

3828 *J. Agric. Food Chem.,* Vol. 49, No. 8, 2001

Pierpoint et al.

$$k_M = k_{exp}/[O_3]_{av} \quad (2)$$

where $[O_3]_{av}$ is the average of the initial and final ozone concentrations, which usually changed by $\leq 15\%$.

Studies in which initial and final ozone concentrations changed by $>15\%$ were disregarded. The pseudo-first-order rate constant, k_{exp}, was determined from linear plots of $\ln([M]_0/[M]_t)$ versus time. The method resulted in good first-order fits, $R^2 > 0.98$, for the compounds studied. Aqueous ozone concentrations were determined using the indigo method ([16]) or through iodometric titration ([17]). In studies involving the direct addition of sodium hydrosulfide to reaction flasks, final ozone concentrations were determined using duplicate flasks.

The relative rate method described by Hoigne and Bader ([14]) was used to measure rate constants that were too fast to observe directly and to provide a direct comparison between anilines with similar substituents. Ozone stock was added to a rapidly stirred approximately equimolar mixture of compound M and a reference compound R. Samples were collected for analysis after the addition of ozone. The rate constant was determined from eq 3

$$k_{rel} = \ln([M]_0/[M]_t)/\ln([R]_0/[R]_t) \quad (3)$$

where M_0 and M_t are the initial and final concentrations, respectively, of compound M and R_0 and R_t are the initial and final concentrations, respectively, of the reference compound.

Analysis. Samples were analyzed directly by HPLC employing a Waters (Milford, MA) model 616 LC and a Millennium system equipped with two 510 pumps, a model 717 autosampler, and a model 996 photodiode array detector. Separations were achieved using a mobile phase of 20−30% acetonitrile in water, at a flow rate of 1.25 mL/min on a Beckman (Fullerton, CA) C-18 (ODS-5 μm), end-capped, 4.6 mm × 25 cm, steel-jacketed column. Peak identification was established by comparison of the retention times and UV spectra with standards.

Nitrite determinations were performed by ion chromatography using a Dionex DX-120 ion chromatograph (Sunnyvale, CA), equipped with an Ionpac AS9-HC column and an AG9-HC guard column, a conductivity detector, an anion self-generating suppressor ARSR II, and Peaknet 5.01 chromatography software. The eluent comprised of 12 mM Na_2CO_3 and 5 mM $NaHCO_3$, at 1.5 mL/min. Peak identification was established by comparison to the retention time of standard samples. For confirmation duplicate samples were collected and analyzed according to the colorimetric method ([16]).

RESULTS AND DISCUSSION

The relative rate data (Table 1) for several substituted anilines have been analyzed with the Hammett relationship

$$\log(k_X/k_H) = \rho\sigma \quad (4)$$

where k_X is the rate constant for the reaction of a meta- or para-substituted benzene derivative, in this case the reaction of ozone with substituted aniline, and k_H is the rate constant for the reaction between ozone and unsubstituted aniline. The substituent constant, σ, is a measure of the electronic effect of replacing H with a given substituent and is, in theory, independent of the nature of the reaction. As substituent constants are not exclusive, their values may be applied to numerous reactions. The slope of the Hammett plot is ρ, referred to as the susceptibility or reaction constant, and is a measure of the sensitivity of the reaction to the effects of electronic perturbation. Thus, the magnitude of ρ provides a measure of the degree to which the reaction responds to substituents. Similarly, when the sign of ρ is positive, the reaction rate is increased by electron

Table 1. Summary of Relative Rate Data and Hammett's Substituent Constants Used in the LFER Plots for the Reaction of Ozone with Substituted Anilines[a]

substituent	σ	F	R	k_X/k_H pH 6	k_X/k_H pH 1.5
3-Me	−0.07	0.01	−0.18	1.34 ± 0.09	1.48 ± 0.09
2-OMe	0.02			1.23 ± 0.09	
4-F	0.06	0.45	−0.39	0.88 ± 0.08	0.7 ± 0.1
4-Cl	0.23	0.42	−0.19	0.74 ± 0.07	2.2 ± 0.1
4-I	0.18	0.42	−0.24	0.66 ± 0.05	2.9 ± 0.2
3-F	0.34	0.45	−0.39	0.58 ± 0.04	1.91 ± 0.07
3-Cl	0.37	0.42	−0.19	0.56 ± 0.05	2.02 ± 0.09
3-I	0.35	0.42	−0.24	0.53 ± 0.04	2.8 ± 0.2
2-F	0.47			0.52 ± 0.05	
3-NO$_2$	0.71	0.65	0.13	0.17 ± 0.02	
4-NO$_2$[b]	1.27	0.65	0.13	0.01 ± 0.002	

[a] The σ, F, and R values were obtained from Hansch et al. ([20]) and Shorter et al. ([21]). [b] Corresponds to σ_p^-.
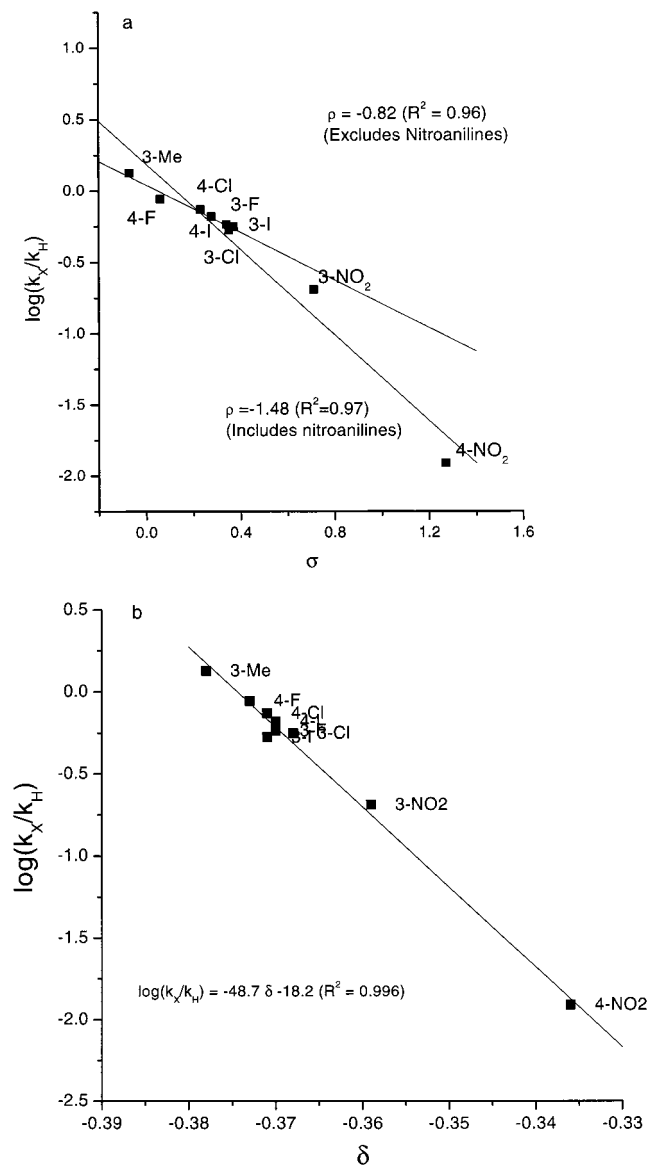

Figure 1. Plot of relative reaction rates at pH 6.5 versus Hammett substituent constants (a) and atomic charges (b).
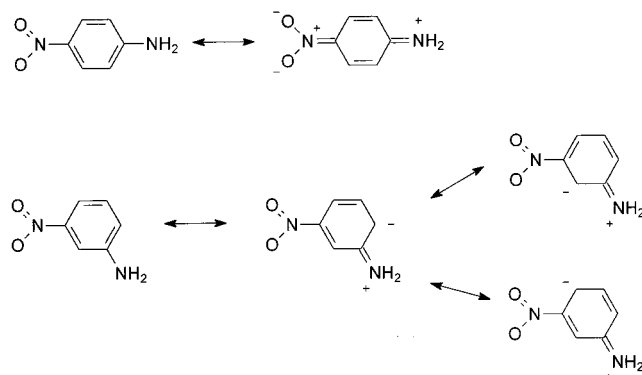
withdrawal, and when it is negative, the reaction rate is increased by electron donation.

Reactions at pH 6.5. At pH 6.5, a linear plot was obtained with $\rho = -1.48$ ($R^2 = 0.973$) (Figure 1a). A departure from Hammett behavior is evident for the

Aniline Ozonation

J. Agric. Food Chem., Vol. 49, No. 8, 2001 **3829**

Table 2. Atomic Charges for Amine Nitrogen[a] and Selected Aromatic Carbons for Substituted Anilines at pH 1.5 and 6.5

| substituent	amine N, pH 6.5	amine N, pH 1.5	carbon, pH 1.5					
			1	2	3	4	5	6
3-Me	−0.375	0.105	−0.168	−0.004	−0.065	0.030	−0.035[b]	−0.013
2-OMe	−0.376							
4-F	−0.373	0.107	−0.188	0.018	−0.076[b]	0.251	−0.076	0.018
4-Cl	−0.371	0.103	−0.165	−0.005	−0.024[b]	−0.054	−0.024	−0.005
4-I	−0.370	0.102	−0.152	−0.018	0.006[b]	−0.174	0.006	−0.018
3-F	−0.370	0.103	−0.141	−0.056	0.198	−0.018	−0.009	−0.024[b]
3-Cl	−0.368	0.105	−0.163	0.000	0.001	0.034	−0.030	−0.006[b]
3-I	−0.374	0.105	−0.176	0.033	−0.227	0.062	−0.042	0.006[b]
2-F	−0.371							
3-NO2	−0.359							
4-NO2	−0.336							

[a] Atomic charge determinations were performed using HyperChem molecular modeling software. [b] Selected ring locations used for correlations at pH 1.5.

Figure 2. Resonance structures of *p*-nitroaniline and *m*-nitroaniline.

Figure 3. Plot of relative reaction rates at pH 6.5 of substituted anilines with atomic charges.

substituents when *m*- and *p*-nitroaniline are not included in the regression; $\rho = -0.82$ ($R^2 = 0.964$). This suggests that *m*- and *p*-nitroaniline were less reactive than predicted. This behavior was particularly evident for *p*-nitroaniline, suggesting that the direct conjugation effects at the reaction center are poorly predicted (Figure 2). The effects of resonance on the Hammett's correlation for reactions of aniline and other similar species, that is, those possessing loosely held lone pairs of electrons coupled with substitutents capable of accepting a pair of electrons via conjugation, are well established (*1−3, 5*). However, the commonly used σ value of 1.27, which extends the range of applicability of the Hammett equation, was insufficient to account for the conjugation effects on ozonation of *p*-nitroaniline. The deviation observed for *m*-nitroaniline is suggestive of similar, although weaker, resonance stabilization (Figure 2b).

The negative ρ values obtained by the plot indicate that the rate-limiting step involves nucleophilic attack; that is, the reaction is electrophilic. Among the substituents used, the observed order of reactivity was 3-CH$_3$ > 2-OCH$_3$ > H > 4-F > 4-Cl > 4-I > 3-F > 3-Cl > 3-I > 2-F > 3-NO$_2$ > 4-NO$_2$. Thus, the addition of electron-withdrawing groups to the benzene ring resulted in decreased reactivity of the substituted aniline.

The electrophilic reaction process is further evidenced by examining a plot of the reactivity data against atomic charges at the amine group (Figure 1b). Atomic charge determinations were performed using the molecular modeling software HyperChem from Hypercube, Inc., Waterloo, ON, Canada. Low potential energy surface conformations of aniline and the series of substituted anilines corresponding to global minimums were determined using molecular mechanics in the MM+ force
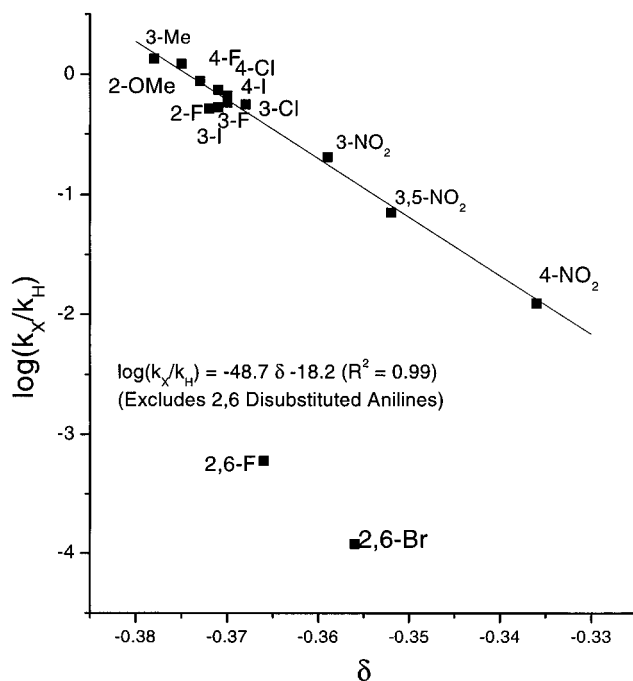
fields, in the gas phase. Structures were further refined and atomic charges determined by geometric optimization and single-point calculations using the semiempirical MNDO and AM1 methods. The conjugate gradient (Polak-Ribiere) method was used as the optimizer with an RMS gradient of 0.01 kcal/Å·mol. Geometric optimizations were made for *p*- and *m*-nitroaniline using resonance structures shown in Figure 2. Single-point calculations using the MNDO method were also performed directly on empirically derived geometric optimizations. The latter method was found to produce the best correlation and was therefore used for comparison to Hammett values (Table 2).

The use of amine group atomic charges showed an improved correlation over Hammett values, with a linear regression equation represented by $\log(k_X/k_H) = -48.7\delta - 18.2$ ($R^2 = 0.996$), where δ is atomic charge. The halogenated substituents were clustered, indicating similar reactivity effects, and both *p*- and *m*-nitroaniline were well predicted, demonstrating that the amine group is the principal reaction site. In Figure 3, ortho- and disubstituted anilines were included. The substituted anilines, 2-methoxyaniline and 3,5-dinitroaniline, were well correlated. 2,6-Difluoroaniline and 2,6-dibro-

moaniline were poorly correlated, possibly due to steric hindrance at the reaction center.

Through the relative rate method and using nitrite as the reference compound, aniline was determined to have a reaction rate of $(14 \pm 3) \times 10^6$ M^{-1} s^{-1} at pH 6.5, 10 mM *tert*-butyl alcohol. Hoigne and Bader (*14*) reported a slightly higher reaction rate for neutral aniline; $k = (90 \pm 20) \times 10^6$ M^{-1} s^{-1}, 10 mM *tert*-butyl alcohol, although their reported pH range was 1.2−2. At pH 2, the amine group of aniline is positively charged; pK_a = 4.6. It is likely that the pH range was reported inaccurately in their study, as anilinium is expected to have a considerably slower reaction rate. In fact, the reaction rate of anilinium, $k = (5.9 \pm 0.9) \times 10^4$ M^{-1} s^{-1} at pH 1.5, was found to be >2 orders of magnitude slower than that of aniline and comparable to those of other aromatics, such as phenol and cresol.

Reactions at pH 1.5. A linear plot of relative rate data versus Hammett constants at pH 1.5 showed poor correlation; $\rho = 0.72$ ($R^2 = 0.572$) (Figure 4a). Generally, the reactivity of the substituted anilines was found to increase with decreasing electron-donating capacity of the meta- and para-substituents, as suggested by the positive slope, indicating a nucleophilic process. Although reactivities were poorly correlated, the observed order was 4-I > 3-I > 4-Cl > 3-Cl > 3-F > 3-CH$_3$ > H > 4-F.

The high slopes associated with respective para- and meta-substituents of fluoro-, chloro-, and iodoaniline indicate strong electronic effects. However, the k_{rel} values for para-substituents of chloro-, fluoro-, and iodoaniline are not indicative of inductive effects of the substituents, when compared to the variation of the meta-halogenated substituents. Para-substituted fluoroaniline was found to have a reaction rate slightly less than that of aniline, whereas chloro- and fluoroaniline had reactivities 2−3 times higher than that of aniline. This was not observed with the meta-halogenated substituents. It is adequate to postulate that in the para position, where the halogens interact with the electron-deficient center through resonance, the resonance and inductive components are of comparable magnitudes. In the case of chlorine, bromine, and iodine, the inductive factors are larger, so that a net electron-withdrawing effect results and the observed reaction rate is somewhat larger. In the case of fluorine, the resonance effect is slightly larger than that of the inductive effect, resulting in a small net electron donation and a corresponding decrease in reaction rate over that of the unsubstituted aniline.

Although poorly correlated, the results of the Hammett analysis suggest that the electronic effects of the substituents are influencing the reaction rates. However, the degree to which the effects are correlated varies depending on the position of the substituent and not, to any significant degree, the individual substituents. Thus, it appears that the reaction sites vary, and these reaction sites are affected by the electronic demands of the substituents.

To confirm this, the data were plotted against atomic charge determinations for the amine group and then for selected reaction sites of the ring. Reaction sites were determined by selecting ring locations with favorable electrostatic potentials.

Figure 4b shows that the amine group atomic charges were poorly correlated. Use of atomic charges at selected ring locations significantly improved the correlation
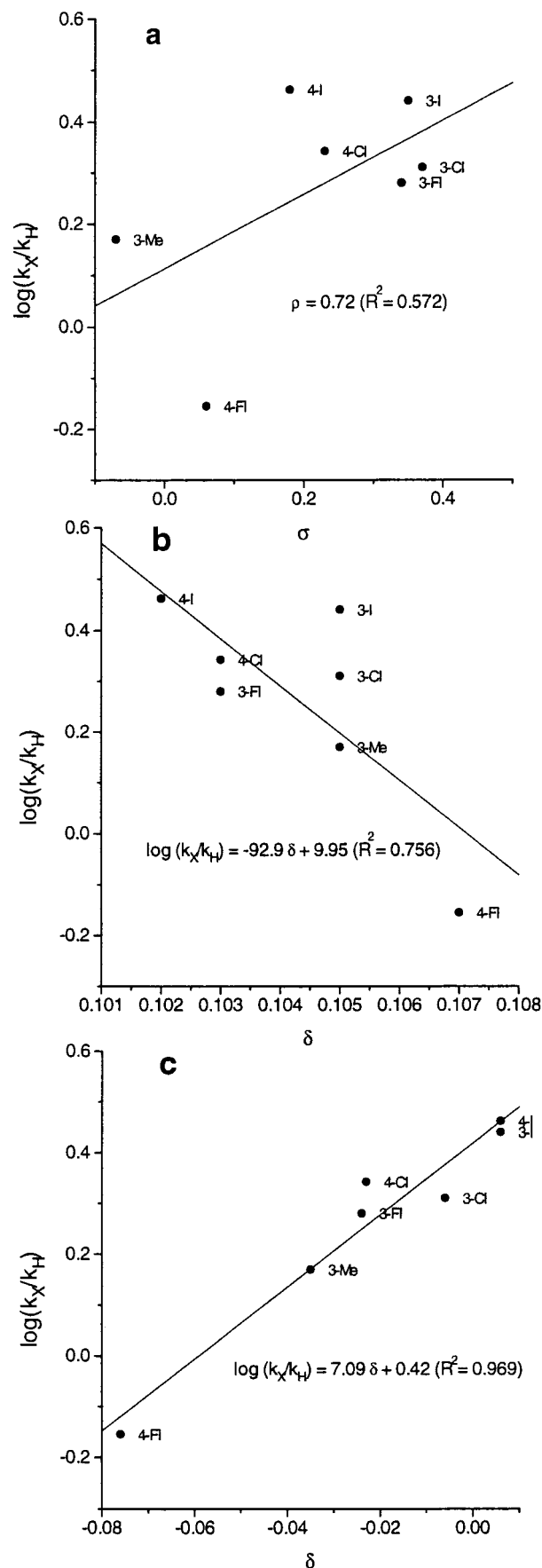

Figure 4. Plot of relative reaction rates at pH 1.5 of substituted anilines with ozone versus Hammett substituent constants (a), amine group atomic charges (b), and selected ring charge atomic charges (c).
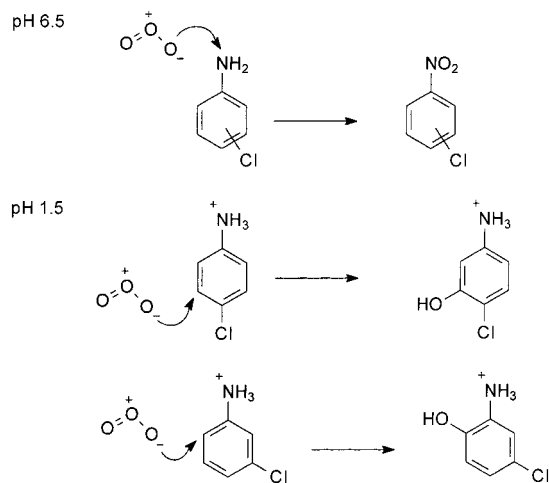
Aniline Ozonation

J. Agric. Food Chem., Vol. 49, No. 8, 2001 **3831**

Figure 5. Reactions of ozone with substituted anilines.

(Figure 4c), suggesting that the initial ozone reaction with the substituted aniliniums occurs at the benzene ring. The low reactivity of the ammonium ion and protonated amino groups (*14*) further suggests reaction at the benzene ring.

From the plot, the global reaction process also appears to be nucleophilic in nature, with reactions of para-halogenated anilines occurring at the meta-position to the amine, and the reactions of meta-halogenated anilines occurring at the ortho-position (Figure 5). Thus, for para-halogenated anilines the electrophilic character of the reaction site is mainly due to the nature of the substituent group that activates the respective ortho-position. The site is deactivated by meta-halogenation.

CONCLUSIONS

Ring substitution and pH effected ozone reaction sites, as well as reaction rates. Reaction rates at pH 1.5 were considerably slower than those at pH 6.5. Initial ozone reactions at high pH occur principally at the amine group, whereas at low pH benzene ring reaction sites are indicated. Thus, although initial ozone reactions with aniline in aqueous solutions at pH 6.5 are expected to result principally in the formation of substituted nitrobenzenes, reactions at pH 1.5 are likely to result in hydroxylation of the benzene ring and possibly 1,3-dipolar addition. Formation of nitrosobenzene and nitrobenzene in neutral aqueous solutions of aniline exposed to ozone have been reported (*18*). The order of reactivity for the reaction of ozone with the substituted anilines was comparable to that of reactions of pyridium chlorochromate with aromatic anils (*19*). At low pH, the inductive effects of the ring substituents appear to influence the location of the ring reactions, with reactions occurring at locations of favorable atomic charge.

Although the selected values for Hammett substituent constants could be improved by further refinement of mesomeric substituents, they provide a good indication of the nature of the ozone reactions. In addition to providing useful information to predict reaction rates, they can also provide an indication of reaction mechanisms. Atomic charge distributions have the benefit of improved correlation and provide a better indication of reaction site. The predictive nature of this method intimates its usefulness in determining the potential effectiveness of ozonation processes for treating waste contaminated with anilines and other benzene derivatives.

The results of this study indicate that for best treatment practices with the goal being minimization of toxic byproduct formation, the process should be conducted under strongly acidic conditions. This favors direct ozonation and thus the formation of hydroxyanilines, known to be less toxic and more readily biodegraded. Under neutral conditions, the breakdown of the aniline pesticide derivatives would be significantly faster, due to the formation of hydroxy radicals, yet this process affords potentially toxic byproducts, that is, nitroanilines.

LITERATURE CITED

(1) Hammett, L. P. The Effect of Structure Upon the Reactions of Organic Compounds. Benzene Derivatives. *J. Am. Chem. Soc.* **1937**, *59*, 96−103.

(2) Jaffe, H. H. A Reexamination of the Hammett Equation. *Chem. Rev.* **1954**, *53*, 191−261.

(3) Brown, H. C.; Okamoto, Y. Substituent Constants for Aromatic Substitution. *J. Chem. Soc.* **1957**, *79*, 1913−1917.

(4) Taft, R. W.; Lewis, I. C. The General Applicability of a Fixed Scale of Inductive Effects. II. Inductive Effects of Dipolar Substituents in the Reactivities of m- and p-Substituted Derivatives of Benzene. *J. Am. Chem. Soc.* **1958**, *80*, 2436−2443.

(5) Biggs, A. I.; Robinson, R. A. The Ionization of Some Substituted Anilines and Phenols. A Test of the Hammett Relation. *J. Chem. Soc.* **1961**, 388−393.

(6) Whitworth, A. J.; Ayoub, R.; Rousseau, Y.; Fliszar, S. Quantitative Investigation of the Ozonolysis Reaction. X. On the Kinetics of the Reaction of Ozone with Ring-Substituted Styrenes in Carbon Tetrachloride Solution. *J. Am. Chem. Soc.* **1969**, *91*, 7128−7131.

(7) Klutsch, G.; Fliszar, S. Quantitative Investigation of the Ozonolysis Reaction. XVII. Relative Rates for the Ozone Attack on Phenylethylenes. *Can. J. Chem.* **1972**, *50*, 2841−2844.

(8) Henry, H.; Zazor, M.; Fliszar, S. Quantitative Investigation of the Ozonolysis Reaction. XVIII. A Kinetic Study of the Ozone Attack on Phenylethylenes. *Can. J. Chem.* **1973**, *51*, 3398−3402.

(9) Murray, R. W.; Iyanar, K.; Lee, C. L.; Chen, J. A Linear Free Energy Study of the Ozonolysis of Ring-Substituted α-Methylstyrenes. *J. Org. Chem.* **1995**, *60*, 5335−5336.

(10) Kearney, P. C.; Kaufman, D. D. *Herbicides: Chemistry, Degradation and Mode of Action*, 2nd ed.; Dekker: New York, 1975.

(11) Sittig, M. *Hazardous and Toxic Effects of Industrial Chemicals*; Noyes Data Corp.: Park Ridge, NJ, 1979.

(12) Essington, M. E. Absorption of Aniline and Toluidines on Montmorillonite. *Soil Sci.* **1994**, *158* (3), 181−188.

(13) Saupe, A.; Wiesmann, U. Ozonation of 2,4-Dinitrotoluene and 4-Nitroaniline as well as Improved Dissolved Organic Carbon Removal by Sequential Ozonation-Biodegradation. *Water Environ. Res.* **1998**, *70* (2), 146−154.

(14) Hoigne, J.; Bader, H. Rate Constants and Reactions of Ozone with Organic and Inorganic Compounds in Water—II. *Water Res.* **1983**, *17*, 185−194.

(15) Staehelin, J.; Hoigne, J. Decomposition of Ozone in Water: Rate of Initiation by Hydroxide Ions and Hydrogen Peroxide. *Environ. Sci. Technol.* **1982**, *16*, 676−681.

(16) Bader; H.; Hoigne, J. Determination of Ozone in Water by the Indigo Method; A Submitted Standard Method. *Ozone Sci. Eng.* **1982**, *4*, 169−176.

(17) Flamm, D. L. Analysis of Ozone at Low Concentrations with Boric Acid Buffered KI. *Environ. Sci. Technol.* **1977**, *11*, 978−983.

3832 *J. Agric. Food Chem.,* Vol. 49, No. 8, 2001

Pierpoint et al.

(18) Chan, W. F.; Larson, R. A. Mechanisms and Products of Ozonolysis of Aniline in Aqueous Solution Containing Nitrite Ion. *Water Res.* **1991**, *25* (12), 1539−1544.

(19) Karunakaran, K.; Nagarajan, S.; Kanagavel, D.; Jegdish, T. N.; Palanisamy, P. N.; Elango, K. P. Interactive Free Energy Relationship on the Oxidation of Aromatic Anilines by Phenyliodoso Acetate. *Oxidation Commun.* **1997**, *20* (4), 576−578.

(20) Hansch, C.; Leo, A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, *91*, 165−195.

(21) Shorter, J.; Phil, D.; Chem, C. *Correlation Analysis of Organic Reactivity*; Research Studies Press: New York, 1982.