

# Organic and Biological Chemistry

## Directive Effects in Electrophilic Aromatic Substitution ("Ipso Factors"). Nitration of Haloanisoles

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**Abstract:** The kinetics of the nitration of anisole and *p*-iodo-, *p*-bromo-, and *p*-chloroanisole have been studied. The relative reactivities of the ortho positions of these compounds are 1:0.119:0.077:0.069. In acetic anhydride attack by NO<sub>2</sub><sup>+</sup> para to the methoxyl occurs to the extent of 30.6, 40, 31, and 28% of total attack. Therefore, *i*<sub>f</sub><sup>R</sup>, the *ipso* partial rate factors for the halogens iodine, bromine, and chlorine, are 0.18, 0.079, and 0.061. These values represent the directive effect of the halogen on the rate of attack, not ortho, meta, or para to the substituent, but directly at the position bearing the substituent.

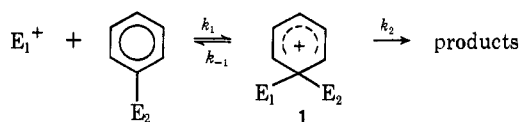
There exists an enormous body of data concerning directive effects in electrophilic aromatic substitution. Not only are substituents classed as activating or deactivating, ortho-para directing or meta directing, but also quantitative measures of these effects have been determined. The directive effects of a substituent, R, are expressed by the partial rate factors, *o*<sub>f</sub><sup>R</sup>, *m*<sub>f</sub><sup>R</sup>, and *p*<sub>f</sub><sup>R</sup>, representing the rates of electrophilic attack at a single position ortho, meta, or para to the substituent, relative to the rate of attack at a single position of benzene.

However, there exist extremely few data concerning the directive effect of the substituent for attack directly at the *ipso* (Latin: itself) position, the position bearing the substituent. This directive effect is analogous to the "element effect"<sup>2</sup> in nucleophilic aromatic substitution. But in the context of electrophilic aromatic substitution, it is appropriate to express such a directive effect quantitatively by an *ipso* partial rate factor ("ipso factor"), determinable by

$$i_f^R = \frac{k_{ArR}^{\text{total}} \sigma_o^R \text{ attack at R}}{k_{ArH}^{\text{total}} \sigma_o^H \text{ attack at H}} \quad (1)$$

As with other partial rate factors, the *ipso* factor *i*<sub>f</sub><sup>R</sup> is characteristic not only of the substituent R but also of the aromatic substrate, the attacking electrophile, and the reaction conditions. Of course, we would expect the *ipso* factors to follow a selectivity relationship.<sup>3</sup>

Electrophilic attack at a substituent other than hydrogen is by no means uncommon. The general form of a reaction involving attack on a substituted benzene may be written



(1) Alfred P. Sloan Research Fellow, 1967-1969.

(2) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Amer. Chem. Soc.*, **79**, 385 (1957).

(3) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

This scheme may lead to any of several different results: (1) the  $\sigma$  complex intermediate (1) may lose E<sub>2</sub><sup>+</sup>, and the net result would be the substitution of one electrophile for another.<sup>4</sup> (2) The substituent, E<sub>2</sub>, may migrate to another position of the aromatic system, with subsequent proton loss, and the net result would be an aromatic rearrangement or isomerization.<sup>5</sup> (3) Some form of the  $\sigma$  complex (1) may be stable, as in the formation of cyclohexadienones from phenols,<sup>6</sup> or other "nonconventional" aromatic reactions.<sup>7</sup> (4) The  $\sigma$  complex (1) may lose E<sub>1</sub><sup>+</sup> and revert to reactants, so that formation of the intermediate would escape detection.

The *ipso* factor of the substituent E<sub>2</sub> is given by the value of *k*<sub>1</sub>, divided by the value of *k*<sub>1</sub> for the reaction in which E<sub>2</sub> is hydrogen. In order that the measured rate of reaction be simply *k*<sub>1</sub>, it is necessary that *k*<sub>-1</sub> be sufficiently small, so that the attack of E<sub>1</sub><sup>+</sup> is effectively irreversible. Therefore *k*<sub>1</sub> is measurable from the rates of suitable reactions of types 1, 2, and 3 above, but not of type 4.

A few *ipso* factors have been determined or may be estimated. It is well known that demetallation can be quite facile (although the extreme reactivity of such organometallics as aryl Grignard reagents must be attributed to incursion of a different mechanism). For example, Eaborn<sup>8</sup> has reported values for *i*<sub>f</sub><sup>MesSi</sup> of ca. 10<sup>5</sup> in protonation and of ca. 10<sup>8</sup> in uncatalyzed bromination. On the other hand, *i*<sub>f</sub><sup>MesSi</sup> is less than 1 in a diazo coupling. Kuivila and Nahabedian<sup>9</sup> have estimated *i*<sub>f</sub><sup>B(OH)<sub>2</sub></sup> = 3-5 in protonation of anisole. de la Mare and Harvey<sup>10</sup> have found that the partial rate

(4) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amsterdam, 1965, Chapters 9 and 10; P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution: Nitration and Halogenation," Academic Press, New York, N. Y., 1959, Chapter 16; D. V. Nightingale, *Chem. Rev.*, **40**, 117 (1947).

(5) M. J. S. Dewar, "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 299-306; L. I. Smith, *Org. React.*, **1**, 370 (1942).

(6) V. V. Ershov, A. A. Volod'kin, and G. N. Bogdanov, *Russ. Chem. Rev.*, **32**, 75 (1963).

(7) E. Baciocchi and G. Illuminati, *Progr. Phys. Org. Chem.*, **5**, 1 (1967).

(8) C. Eaborn, "Organosilicon Compounds," Butterworths, London, 1960, pp 156-157.

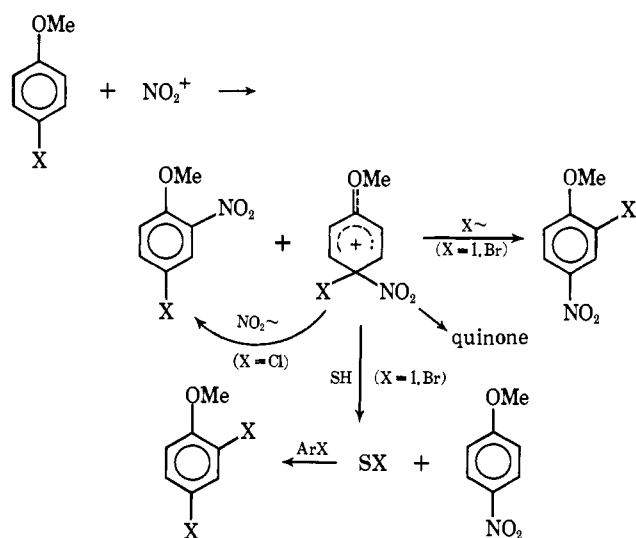
(9) H. G. Kuivila and K. V. Nahabedian, *J. Amer. Chem. Soc.*, **83**, 2159 (1961).

factor for acid-catalyzed bromode(*tert*-butylation) of *tert*-butylbenzene is 1.4. Stock and Brown<sup>11</sup> and de la Mare and Johnson<sup>12</sup> have found similar values for chlorode(*tert*-butylation) of some substituted *tert*-butylbenzenes. From Arnett and Klingensmith's data<sup>13</sup> on the bromination of anisole and *p*-methoxybenzhydrols, values of 0.051 and 0.011 may be estimated for  $i_f^{p\text{-MeOC}_6\text{H}_4\text{CHOH}}$  and  $i_f^{p\text{-O}_2\text{NC}_6\text{H}_4\text{CHOH}}$ , if it is assumed that the salt effect on the kinetics of bromination of anisole is the same as that on the bromination of a substituted *p*-methoxybenzhydrol. Baciocchi and Illuminati<sup>14</sup> have determined  $i_f^{\text{CH}_3} = 0.29$ ,  $i_f^{\text{tert-Bu}} = 0.25$ , and  $i_f^{\text{Br}} < 2 \times 10^{-7}$  for bromination of 4-substituted 2,6-di-*tert*-butylphenols in 98% aqueous acetic acid. From the data of Batts and Gold,<sup>15</sup> a value of  $2.64 \times 10^{-2}$  may be calculated for  $i_f^{\text{I}}$  in protonation of 1,3,5-trimethoxybenzene. Longridge and Long<sup>16</sup> have estimated that  $i_f^{\text{COOH}} = 2 \times 10^{-3}$  in protodecarboxylation of azulene-1-carboxylic acid.

From the few available data it is not possible to develop a complete theory of such substituent effects. Even the current deep level of understanding of ortho, meta, and para directive effects does not permit prediction of *ipso* factors, nor can we readily rationalize the values observed. Therefore we are undertaking to determine *ipso* factors for many of the common substituents, in the hope of elucidating their determinants.

In this paper we seek to establish the *ipso* factors in acetyl nitrate nitration ( $E_1 = \text{NO}_2$ ) for the three displaceable halogen substituents, iodo, bromo, and chloro ( $E_2 = \text{X}$ ). In order to facilitate attack at the *ipso* position (that bearing the substituent) we have chosen the *p*-haloanisoles as substrates. In the Discussion we justify our assumption that when  $E_1 = \text{NO}_2$  and  $E_2 = \text{I}$  or  $\text{Br}$ ,  $k_2 \gg k_{-1}$ ; the situation with  $E_1 = \text{NO}_2$  and  $E_2 = \text{Cl}$  is also considered in some detail.

Previous studies<sup>17-22</sup> of the nitration of halophenol derivatives have demonstrated that *ipso* attack at iodine and bromine is quite possible. The halogen may then migrate to another position of the ring (the Reverdin rearrangement<sup>19,20</sup>) or may be liberated to halogenate solvent or another molecule of substrate.<sup>22</sup> No evidence of *ipso* attack of  $\text{NO}_2^+$  at chlorine has ever been obtained, since nitration of *p*-chlorophenyl ethers was found to be quite normal.<sup>21</sup> However, by comparison with model compounds,<sup>23</sup> we should not expect chlorine migration to be more facile than nitro migration, although quinone formation is quite possible. We may summarize the reactions to be expected from nitration of a *p*-haloanisole. Under our reaction conditions, we have found that rearranged product is not formed, but that iodine or bromine is liberated and rapidly halo-



genates another molecule of reactant. This secondary reaction must be taken into account in the kinetic expressions.

## Results

**Product Distributions.** Table I lists the percentages of *p*-nitroanisole formed in nitrations in acetic anhydride. Values are averages of several runs, and ratios

Table I. Percentage of *p*-Nitroanisole in Products from Nitration of *p*-XC<sub>6</sub>H<sub>4</sub>OMe

X	In Ac <sub>2</sub> O	In aqueous HOAc
H	30.6	40
I	40	
Br	31	39 <sup>a</sup>
Cl	<0.3	37 <sup>b</sup>

<sup>a</sup> *p*-Nitroanisole plus nitrophenols relative to 4-bromo-2-nitroanisole (excluding 2,4-dibromoanisole). <sup>b</sup> 4-Chloro-2-nitrophenol. See Discussion.

did not vary by more than  $\pm 2\%$  from run to run or from point to point during a run. The presence of 0.01 *M* lithium chloride in the nitrating mixture did not change the ratios. The ortho/para ratio for the nitration of anisole agrees with published values.<sup>24</sup> For comparison, the percentages of para attack in nitration in aqueous acetic acid are also included in Table I. For each mole of *p*-nitroanisole formed in the nitration of *p*-iodo- and *p*-bromoanisole, nearly 1 mol of 2,4-dihaloanisole was also detected. (This stoichiometry has also been observed in the nitration of 2-iodothiophene.<sup>25</sup>) No anisole or *o*-nitroanisole was detected in such nitrations; therefore formation of *p*-nitroanisole does not occur *via* protodehalogenation followed by nitration of the resulting anisole.

The only products from the nitration of *p*-chloroanisole in acetic anhydride were 4-chloro-2-nitroanisole and a small amount (*ca.* 1%, but variable) of 4-chloro-2,6-dinitrophenol. However, as the water content of the nitrating medium increased, the amount of phenol increased, up to a maximum of 37% in 10 *M*  $\text{HNO}_3$  solutions containing at least 11 *M*  $\text{H}_2\text{O}$ .

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(25) M. Markovitz, Ph.D. Thesis, New York University, 1963; *Diss. Abstr.*, 24, 3100 (1964).

(10) P. B. D. de la Mare and J. T. Harvey, *J. Chem. Soc.*, 131 (1957).

(11) L. M. Stock and H. C. Brown, *J. Amer. Chem. Soc.*, 81, 5615 (1959).

(12) P. B. D. de la Mare and E. A. Johnson, *J. Chem. Soc.*, 4076 (1963).

(13) E. M. Arnett and G. B. Klingensmith, *J. Amer. Chem. Soc.*, 87, 1032, 1038 (1965).

(14) E. Baciocchi and G. Illuminati, *ibid.*, 89, 4017 (1967).

(15) B. D. Batts and V. Gold, *J. Chem. Soc.*, 4284, 5753 (1964).

(16) J. L. Longridge and F. A. Long, *J. Amer. Chem. Soc.*, 90, 3092 (1968).

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(20) F. Reverdin and F. Düring, *ibid.*, 32, 152 (1899).

(21) F. Reverdin and F. Eckhard, *ibid.*, 32, 2622 (1899).

(22) G. M. Robinson, *J. Chem. Soc.*, 109, 1078 (1916).

(23) C. L. Perrin, *J. Org. Chem.*, 36, 420 (1971).

Table II. Relative Reactivities of Ortho Positions of Para-Substituted Anisoles

[C <sub>6</sub> H <sub>5</sub> OMe]	[ <i>p</i> -IC <sub>6</sub> H <sub>4</sub> OMe]	[AcONO <sub>2</sub> ]	[Adduct] <sup>a</sup>	$m_t^I$
0.25	0.25	0.50	$0.2 \times 10^{-2}$	0.116
0.25	0.25	0.50	$1 \times 10^{-2}$	0.112
0.125	0.50	0.50	$1 \times 10^{-2}$	0.121
0.25	0.25	0.50	$1 \times 10^{-2}$ <sup>b</sup>	0.125
0.06	0.60	0.50	$4 \times 10^{-2}$	0.120
0.06	0.60	0.40	$4 \times 10^{-2}$	0.117
				Av 0.119 ± 0.004
[ <i>p</i> -IC <sub>6</sub> H <sub>4</sub> OMe]	[ <i>p</i> -BrC <sub>6</sub> H <sub>4</sub> OMe]	[AcONO <sub>2</sub> ]	[Adduct] <sup>c</sup>	$m_t^I/m_t^{Br}$
0.15	0.15	0.15	$5.9 \times 10^{-5}$	1.53
0.30	0.30	0.15	$5.9 \times 10^{-5}$	1.63
0.15	0.15	0.225	$5.9 \times 10^{-5}$	1.51
0.30	0.075	0.15	$5.9 \times 10^{-5}$	1.59
0.075	0.30	0.15	$5.9 \times 10^{-5}$	1.46
0.15	0.15	0.20	$5.9 \times 10^{-5}$	1.43
				Av 1.53 ± 0.07
[ <i>p</i> -IC <sub>6</sub> H <sub>4</sub> OMe]	[ <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> OMe]	[AcONO <sub>2</sub> ]	[Adduct] <sup>c</sup>	$m_t^I/m_t^{Cl}$
0.15	0.15	0.20	$5.9 \times 10^{-5}$	1.14
0.075	0.30	0.18	$5.9 \times 10^{-5}$	1.33
				Av 1.24 ± 0.10

<sup>a</sup> Lithium nitrate; also 0.02 *M* urea. See Experimental Section. <sup>b</sup> Also 0.01 *M* lithium chloride. <sup>c</sup> Sulfuric acid; also 0.001 *M* urea. See Experimental Section.

**Kinetic Orders.** At anisole or *p*-iodoanisole concentrations of *ca.* 0.25 *M*, the initial rate of nitration was observed to be zero order in substrate and of a high order in nitric acid, and both these substrates react at the same rate. Fischer, Read, and Vaughan<sup>26</sup> have observed similar behavior in nitration of xylenes with acetyl nitrate. At lower concentrations the rate appeared to be first order<sup>27</sup> in substrate, although the data are somewhat erratic from run to run. Therefore all relative reactivities were determined by competitive nitrations of pairs of substrates. That the relative reactivities were found to be independent of the concentrations of the substrates demonstrates that the product-determining step is always first order in aromatic.

**Relative Reactivities and *Ips*o Factors.** The relative reactivities of the anisoles are indicated in Table II. These values were obtained by pairwise comparison under competitive conditions, as indicated. They are reported in terms of the meta partial rate factors for the halogens (the reactivities of an ortho position of the *p*-haloanisole, relative to an ortho position of anisole), since the relative reactivities were determined by following formation of ortho-nitrated anisoles, the normal products. For example, an ortho position of *p*-iodoanisole is only 0.119 times as reactive as an ortho position of anisole, so  $m_t^I = 0.119$  describes the deactivation of the position meta to the iodine. Likewise, an ortho position of *p*-iodoanisole is 1.53 times as reactive as an ortho position of *p*-bromoanisole, so  $m_t^I/m_t^{Br} = 1.53$  describes the reactivity at a position meta to an iodine relative to one meta to a bromine. Therefore the deactivation of a position meta to a bromine is given by  $m_t^{Br} = 0.077$ .

The relative reactivities,  $m_t^I = 0.119$ ,  $m_t^{Br} = 0.077$ , and  $m_t^{Cl} = 0.096$ , are significantly different from the values<sup>3</sup> 0.0112, 0.0010, and 0.00084, respectively, found in the nitration of the halobenzenes with nitric acid in nitromethane. However, it is to be expected that nitration of substituted anisoles will be a less selective process than nitration of substituted benzenes, since a

halogen substituent will be less deactivating when a methoxy substituent is present to accept much of the positive charge.

The apparent reversal of the partial rate factors of Br and Cl is noteworthy. However, 4-chloro-2-nitroanisole is formed from *p*-chloroanisole by two independent paths—not only by the normal attack of NO<sub>2</sub><sup>+</sup> at the ortho position but also by the *ipso* attack at the para position, followed by rearrangement of the nitro group to the ortho position. This statement is justified in the Discussion. Thus the reactivity of the ortho position appears greater than it really is, since the apparent  $m_t^{Cl}$  is in fact equal to  $m_t^{Cl} + i_t^{Cl}/r_H$ , where  $r_H$  is the ortho/para ratio in anisole. To determine  $i_t^{Cl}$ , it is necessary to determine what fraction of the 4-chloro-2-nitroanisole arises *via* para attack and rearrangement. Fortunately, para attack manifests itself through demethylation and production of 4-chloro-2-nitrophenol or 4-chloro-2,6-dinitrophenol. From the extent of demethylation, we conclude that the ortho/para ratio in *p*-chloroanisole is 63/37 in aqueous acetic acid. The justification for this value is presented in the Discussion.

In order to estimate the extent of para attack on *p*-chloroanisole in acetic anhydride, it is necessary to apply a small correction for the increase of the ortho/para ratio generally observed on going to acetic anhydride. We have determined that this ratio in anisole and *p*-bromoanisole increases from 60/40 to 69.4/30.6 and from 61/39 to 69/31, respectively. If we assume that this same solvent effect on the ortho/para ratio is operative for *p*-chloroanisole, we may estimate that the ortho/para ratio in *p*-chloroanisole would increase to 72/28 in acetic anhydride.

Therefore the true  $m_t^{Cl}$  is not 0.096, but only 0.069, since 28% of the 4-chloro-2-nitroanisole arises *via* para attack and rearrangement. Thus we find that there is in fact no reversal of the meta partial rate factors of Cl and Br.

Given the ratios of ortho to para attack on the anisoles, and the reactivity of the ortho position of the *p*-haloanisole, relative to that of the ortho position of anisole, we may calculate (see Experimental Section) the reactivity of the para position of the *p*-haloanisole,

(26) A. Fischer, A. J. Read, and J. Vaughan, *J. Chem. Soc.*, 3691 (1964).

(27) M. A. Paul, *J. Amer. Chem. Soc.*, 80, 5329 (1958).

**Table III.** *Ips*o Factors for the Halogens, in the Nitration of *p*-Haloanisoles in Acetic Anhydride

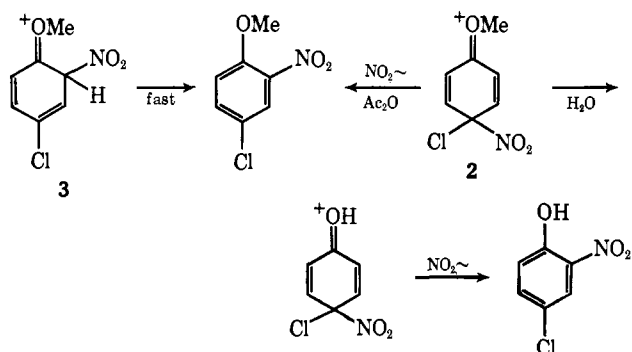
X	$i_t^X$
I	0.18
Br	0.079
Cl	0.061

relative to that of the para position of anisole, which is just the desired *ipso* factor of the halogen. These *ipso* factors are listed in Table III.

### Discussion

We must justify our assumption that attack of nitronium ion is the product-determining step in reactions of *p*-iodo- and *p*-bromoanisole, and that the relative rates that we measure do not also reflect the leaving ability of positive iodine or bromine. On the basis of hydrogen isotope effects and/or reactivities of model compounds, the relative leaving abilities of the electrophiles of interest increase in the order<sup>23</sup>  $\text{Cl}^+ < \text{NO}_2^+ < \text{Br}^+ < \text{I}^+ \sim \text{H}^+$ . Therefore we may conclude that in nitrodeiodination or nitrodebromination  $k_2 \gg k_{-1}$ ; the product-determining step is attack of nitronium ion, with no appreciable reversibility of this step. Further support for this conclusion comes from our observation that the percentage of nitrodehalogenation product does not increase in the presence of added chloride, which would increase  $k_2$ .

On the other hand, the intermediate (2), which results from *ipso* attack at chlorine, would not be expected to undergo loss or migration of chlorine, since the model compound, 1-chloro-1-nitro-2-keto-1,2-dihydronaphthalene, undergoes acid-catalyzed nitro rearrangement (and, to a much lesser extent, some denitration, which we neglect in our calculations).<sup>23</sup> Thus we surely cannot conclude that the absence of *p*-nitroanisole means that chlorine strongly deactivates *ipso* attack. We would expect the intermediate (2) to undergo nitro rearrangement and formation of 4-chloro-2-nitroanisole, the product that results directly from the "normal" ortho attack. In this case, there is no way of



establishing that *ipso* attack has occurred, or of determining its extent, since it does not lead to distinguishable products. Indeed, this is the situation in acetic anhydride, where only 4-chloro-2-nitroanisole (along with a small amount of 4-chloro-2,6-dinitrophenol) is formed, even though some is formed *via* initial *ipso* attack, followed by nitro rearrangement.

Nevertheless, it is possible to trap this intermediate (2). As the nitrating medium becomes more aqueous, we have found that more and more phenolic product

(4-chloro-2-nitrophenol in aqueous acetic acid, which is a poorer nitrating medium than acetic anhydride) is formed, up to a maximum of 37% in 10 *M*  $\text{HNO}_3$  solutions containing at least 11 *M*  $\text{H}_2\text{O}$ . We contend that phenol is formed only from this intermediate (2), and that we may use the maximum extent of phenol formation to measure the extent of *ipso* attack in *p*-chloroanisole. Our justification for this argument is based on the following observations. Both reactant *p*-chloroanisole and "normal" product 4-chloro-2-nitroanisole are stable to demethylation under the reaction and work-up conditions. This result has been used previously to argue that demethylation in nitration *via* nitrosation occurs at the stage of an intermediate in the reaction.<sup>28</sup> However, it seems likely that this intermediate is the nitrosoanisole,<sup>29</sup> rather than a  $\sigma$  complex, since we have found that no phenols are produced in nitration of anisole or *p*-iodoanisole by  $\text{NO}_2^+$  in aqueous acetic acid. These results are reasonable, since removal of  $\text{H}^+$  or  $\text{I}^+$  is faster than migration of  $\text{NO}_2$ , and thus occurs in preference to demethylation. Also, these results strongly support our implicit assumption that 4-chloro-2-nitrophenol does not arise from demethylation of the  $\sigma$  complex formed by ortho attack (3), since the substituent para to the methoxyl should not exert a strong influence on the competition between demethylation of 3 and proton removal from 3. Strong evidence is the fact that nitration of *p*-bromoanisole in aqueous acetic acid leads to 4-bromo-2-nitroanisole, 4-nitroanisole, 2,4-dibromoanisole, *p*-nitrophenol, and a small amount of 2-bromo-4-nitrophenol, but no 4-bromo-2-nitrophenol. This result demonstrates that demethylation is associated only with attack at a carbon bearing an electrophile that is not readily lost. Finally, since increasing the water content of the nitrating medium beyond 11 *M* does not lead to more than 37% phenol, we may be confident that all the intermediate (2) is being trapped before it undergoes  $\text{NO}_2$  rearrangement. Therefore we conclude that with  $\text{NO}_2^+$  in aqueous acetic acid, *p*-chloroanisole undergoes 37% para attack and 63% ortho attack.

Thus we conclude that the values listed in Table III are truly the *ipso* factors for the halogens. These represent the directive effect of the halogen toward *attack* of  $\text{NO}_2^+$  at the position bearing the halogen, and do not depend on the rates of subsequent reactions of the  $\sigma$  complex intermediate (1).

It is clear from these results that the halogens deactivate the *ipso* position, just as they do the other positions. This is perhaps not surprising for an electron-withdrawing substituent, although if deactivation of the *ipso* position by halogens is to be attributed to the electron-withdrawing power of the halogens, then Baccocchi and Illuminati's<sup>14</sup> values of 0.25 and 0.29 for *ipso* factors of electron-donating<sup>10</sup> alkyl groups must be attributed to some other effect. Also, a remarkable point is that in acetic anhydride  $i_t^{\text{I}} > m_t^{\text{I}}$  and  $i_t^{\text{Br}} \gtrsim m_t^{\text{Br}}$ , as is clear simply from the product ratios reported in Table I. Thus, although these halogens are deactivating, they deactivate the remote meta position slightly more than they deactivate the adjacent *ipso* position. This result is clearly in contrast with the expectation that "at [the *ipso* position], polar effects should be

(28) C. A. Bunton, *et al.*, *J. Chem. Soc.*, 262 (1950).

(29) J. T. Hays, E. H. de Butts, and H. L. Young, *J. Org. Chem.*, 32, 153 (1967).

stronger than those observed were the [halogen] located in any other position of the ring relative to the reaction site."<sup>14</sup>

Another remarkable feature is that these *ipso* factors are not very small. The halogens are indeed deactivating toward *ipso* attack, but not overwhelmingly so. Of course, this feature is due to the fact that nitration of an anisole is quite an unselective reaction, with a small reaction constant  $\rho$ . Also, in the transition state, most of the positive charge resides on the methoxyl oxygen, so that other ring substituents can exert only a small influence. Thus we would invoke differences in selectivity to rationalize the difference between our  $i_f^I = 0.18$  and Batts and Gold's<sup>15</sup>  $i_f^I = 0.0264$  and between our  $i_f^{Br} = 0.08$  and Baciocchi and Illuminati's<sup>14</sup>  $i_f^{Br} < 2 \times 10^{-7}$ . Indeed, we were fortunate in choosing these very reactive substrates, which show appreciable *ipso* attack; preliminary results<sup>30</sup> suggest that *ipso* factors of halogens are much smaller in the more selective nitration of toluenes.

Further research into *ipso* factors is clearly necessary for understanding of them to develop. We hope that we have at least presented the problem and indicated the questions that may be asked and answered. We hope that these initial results will stimulate chemists to elucidate the determinants of *ipso* factors, in terms of inductive, resonance, hyperconjugative, steric, and bond-strength effects. Finally, we suggest that explicit considerations of *ipso* reactivity will help to clarify some features of electrophilic aromatic substitution.

## Experimental Section

**Materials.** Nitrating mixtures were prepared from Eastman White Label acetic anhydride and reagent grade chemicals, without further purification. Use of redistilled acetic anhydride had no effect on the results. The vpc and tlc standards—2,4- and 3,4-chloronitroanisoles,<sup>31,32</sup> 2,4- and 4,2-bromonitroanisoles,<sup>33,34</sup> 2,4-diiodoanisole,<sup>35</sup> 4-iodo-2-nitroanisole,<sup>36</sup> and 2,4- and 4,2-bromonitrophenols<sup>37</sup>—were prepared by published procedures. The other substituted anisoles and phenols, used as substrates or as chromatography standards, were commercially available products, purified if necessary.

**Kinetics.** All reactions were carried out in a  $25.00 \pm 0.03^\circ$  water bath. Urea was included in the nitrating mixtures in order to destroy oxides of nitrogen and avoid nitration *via* nitrosation.<sup>28</sup> The rate of reaction was adjusted for convenience by inclusion of sulfuric acid or lithium nitrate.<sup>27</sup>

A typical kinetic procedure was as follows. A  $4 \times 10^{-2}$  M solution of urea in acetic anhydride was slowly added<sup>38</sup> to a solution of 0.034 g of lithium nitrate in 2.250 g of 70% nitric acid at  $0^\circ$ . The solution was finally made up to 25 ml at  $25^\circ$ . A 10-cc aliquot of this solution was mixed at  $25^\circ$  with 10 cc of an acetic anhydride solution 0.500 M in anisole and 0.500 M in *p*-iodoanisole. Aliquots (1.000 ml) were withdrawn at intervals and added to 20 ml of distilled water plus 5 ml of ether containing 10.0 mg of 4-chloro-2-nitroanisole. After standing 1 hr with occasional shaking, the layers were separated. The aqueous layer was extracted with 5 ml more ether, and the combined ether extracts were washed twice with aqueous sodium carbonate, once with water, and once with saturated aqueous sodium chloride. Most of the ether was then

evaporated, and a 6–7- $\mu$ l portion of the residue was injected into the vpc for analysis.

**Analyses.** All vpc analyses were obtained on an Aerograph 202 dual-column instrument equipped with TC detectors. A 5 ft  $\times$  0.25 in. column of 5% poly(*m*-phenyl ether) (five-ring) on Chromosorb G-AW/DMCS was used at  $200^\circ$  and a helium flow rate of 60 ml/min. Under these conditions all peaks were suitably resolved.

The detector response to each compound was determined empirically. The composition of each sample was determined by comparison of peak heights with the peak height due to a known amount of an internal standard added to the reaction aliquot.

Material balance to better than 5% was obtained for all reaction mixtures subjected to work-up procedures designed to avoid evaporation of volatile reactants. Usually no precautions were taken in evaporating the ether, since all kinetic analyses were based upon rates of formation of *ortho*-nitro products.

Thin layer chromatography on Eastman Chromagram SiO<sub>2</sub> sheets, with ethyl acetate eluent and NH<sub>3</sub> developer, was found to be suitable for resolving nitrophenols of interest. Uv-visible spectra were taken on a Cary 14 spectrophotometer.

**Products from Nitration of *p*-Chloroanisole.** The only volatile product from the nitration of *p*-chloroanisole in acetic anhydride was 4-chloro-2-nitroanisole. No *p*-nitroanisole, 2,4-, 3,4-, or 4,3-chloronitroanisole was detected; vpc would have detected these had they been present to the extent of 0.3% of the product. Even in the presence of 0.04 M LiCl or 0.02 M Bu<sub>4</sub>NCl no *p*-nitroanisole was detected, although some 2,4-dichloroanisole was formed, since some of the chloride was converted to a chlorinating agent, perhaps nitryl chloride.<sup>39</sup> No quinones or acetates were detected by ir analysis of a CCl<sub>4</sub> solution of the product. However, under the reaction and work-up conditions, *p*-benzoquinone is almost entirely converted to a mixture of 2-hydroxy- and 2,5-dihydroxybenzoquinones, identified from the uv spectrum of the aqueous extracts. Nevertheless, the aqueous extracts of the *p*-chloroanisole reaction mixtures showed no peaks due to these species.

Some 4-chloro-2,6-dinitrophenol was isolated from the sodium carbonate extract, whose absorption at 445 nm indicated that about 1% of this product had been formed. Reverdin and Eckhard<sup>21</sup> and Bunton, *et al.*,<sup>28</sup> have also isolated this product. Tlc of the acidified carbonate extract showed that this was the only phenolic material formed.

As the nitrating medium became more aqueous, the yield of nitrophenol increased, up to 37% of the total product, in 10 M HNO<sub>3</sub> solutions containing at least 11 M H<sub>2</sub>O. The following procedure is typical. To 11.0 ml of an acetic acid solution 10.6 M in HNO<sub>3</sub>, 14.7 M in H<sub>2</sub>O, and 0.02 M in urea nitrate, chilled in ice, was added 1.00 ml of a 2.00 M solution of *p*-chloroanisole in acetic acid. The mixture stood several hours at  $0^\circ$  and was then allowed to warm to room temperature overnight. Work-up as above gave a carbonate extract whose absorption at 425 nm indicated that a 36.9% yield of 4-chloro-2-nitrophenol had been formed. Acidification precipitated 4-chloro-2-nitrophenol, mp and mmp 86–87°, single spot on tlc. Vpc of the remaining ether solution showed that 4-chloro-2-nitroanisole was still the only volatile product.

Under the identical reaction and work-up conditions, 4-chloro-2-nitroanisole is not cleaved to phenol or nitrated further, nor is *p*-chloroanisole cleaved by 7.0 M H<sub>2</sub>SO<sub>4</sub> in aqueous acetic acid.

**Products from Other Nitrations in Aqueous Acetic Acid.** To 47.0 ml of an acetic acid solution 9.8 M in HNO<sub>3</sub>, 12.0 M in H<sub>2</sub>O, and 0.17 M in urea nitrate (some suspended), chilled in ice, was added, with stirring, 1.00 ml of a 2.00 M solution of anisole in acetic acid. The mixture was stirred at  $0^\circ$  for 1 hr, at which time it was yellow, rather than the intense violet that results when nitration occurs *via* nitrosation. The product was then poured into water and was worked up as above. The absorption spectrum of the carbonate extract indicated that less than 1% of the product was phenolic. Vpc of the remaining ether solution showed that the *ortho*/*para* ratio was 1.51.

To 55 ml of an acetic acid solution 9.4 M in HNO<sub>3</sub>, 14.7 M in H<sub>2</sub>O, and 0.07 M in urea nitrate were added 3.74 g of *p*-bromoanisole and 2 ml of HOAc. The mixture was held at  $0^\circ$  for 64 hr, and was then poured into water and worked up as above. Tlc of the acidified carbonate extract showed the presence of *p*-nitrophenol, plus a little 2-bromo-4-nitrophenol. The absorption spectrum indicated that 5.6% of the reactant had been converted

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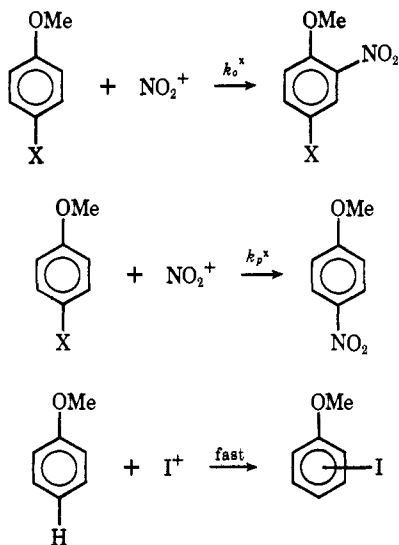
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to 4-nitrophenols and that very little (<0.1%) of any 2-nitrophenol was present. Vpc of the remaining ether solution showed *p*-bromoanisole, *p*-nitroanisole, 2,4-dibromoanisole, and 4-bromo-2-nitroanisole in the ratio 1.000:0.118:0.208:0.344, corresponding to yields of 56.8 (unreacted), 6.7, 11.8, and 19.5%, respectively. Therefore the ratio of 4-bromo-2-nitroanisole to the sum of the 4-nitro products is 19.5:12.3, or 61:39.

**Treatment of Kinetic Data.** For the competitive nitration of anisole and *p*-iodoanisole, the reactions are shown (X = H or I),



Solution of these equations leads to a relationship between the amounts of *o*-nitroanisole (ONA) and 4-iodo-2-nitroanisole (INA), as a function of the ratio  $(k_o^H + k_p^H)/k_o^I$ . In particular, it can be shown that

$$x \left\{ \frac{[\text{ONA}]}{f_o^H} + r_p^I [\text{INA}] - [\text{A}]_0 \right\} + [\text{IA}] \times \left\{ \left( \frac{[\text{A}]_0}{[\text{IA}]_0} \right)^x + r_p^I \right\} \left( \frac{[\text{IA}]}{[\text{IA}]_0} \right)^x - r_p^I \right\} = 0$$

where  $x = (k_o^H + k_p^H)/k_o^I - 1$ ,  $f_o^H = k_o^H/(k_o^H + k_p^H)$ ,  $r_p^I = k_p^I/k_o^I$ ,  $[\text{A}]_0$  and  $[\text{IA}]_0$  are initial concentrations of anisole and *p*-iodoanisole, respectively, and  $[\text{IA}] = [\text{A}]_0 - [\text{INA}]$ . The ratios  $f_o^H$  and  $r_p^I$  were determined from ortho/para product ratios in nitrations of anisole and *p*-iodoanisole alone. A digital computer program was devised to handle the nonlinear least-squares analysis to determine the best value of  $x$  to fit the experimental data. Algebraic manipulation then leads to  $k_o^I/k_o^H = m_t^I$  and to the desired ratio  $k_p^I/k_p^H = i_t^I$ . For example, in the first run of Table II, the best value of  $x$  was 11.46, so  $(k_o^H + k_p^H)/k_o^I = 12.46$ . Using the fraction of ortho attack on anisole,  $k_o^H/(k_o^H + k_p^H) = 0.694$ , we may calculate that  $k_o^H/k_o^I = 8.6$ , or  $m_t^I = 0.116$ . The average  $m_t^I$ , from the six runs of Table II, is 0.119. Therefore, since the ortho/para ratio for *p*-iodoanisole,  $k_o^I/k_p^I$ , equals 60/40, we may calculate  $k_p^I/k_p^H = i_t^I = 0.119 \times (0.694/0.306) \times (0.40/0.60) = 0.18$ . Details are available on request.

The haloanisoles react at nearly the same rates, so that relative reactivities of their ortho positions could be determined simply by comparing initial rates of ortho-nitro product formation. Then from the product ratios these meta factors could be converted to *ipso* factors. For example, in the antepenultimate run of Table II, with equal initial concentrations of *p*-iodoanisole and *p*-bromoanisole, the initial rate of formation of 4-iodo-2-nitroanisole was 1.43 times that of 4-bromo-2-nitroanisole. Such relative rates, along with  $m_t^I = 0.119$ , give  $m_t^{\text{Br}} = 0.077$ . And since the ortho/para ratio for *p*-bromoanisole,  $k_o^{\text{Br}}/k_p^{\text{Br}}$ , equals 69/31, we may calculate  $k_p^{\text{Br}}/k_p^H = i_t^{\text{Br}} = 0.077 \times (0.694/0.306) \times (0.31/0.69) = 0.079$ .

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