tensities. The absorptions assigned to the carbons of the functional groups are generally similar to the chemical shift ranges for the acyclic systems. The methoxyl group of the ester functions absorbs at an average value of 51.5 ± 0.2 ppm and the ether methoxyl at 56.6 ± 0.5 ppm. Analogously, the absorptions of the carbonyl function for the 1,2-diesters were observed at slightly lower field (174.1 ppm average) than those of the 1,3-diesters (175.9 ppm average).

The shielding results for the alicyclic diesters and methoxy esters also follow the general trends established from the acyclic derivatives, although comparisons with the dimethyl-substituted alkanes can only be made for the cyclopentane and cyclohexane derivatives. Large deviations from predicted values based on acyclic substituent effects may result from conformational effects, intramolecular interactions, and variations in C–C–H and C–C–$CO_2R$ bond angles, all of which are interrelated. The limited amount of information available does not allow a determination of the importance of each of these contributions at the present time.

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# Multiple Regression Analysis of Carbon-13 Chemical Shifts and Carbon-13 Proton Coupling Constants in Ortho-Substituted Aromatics

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Carbon-13 proton coupling constants for off-ring C–H bonds in eight ortho-substituted aromatic systems have been correlated with the divided substituent constants $\sigma_I$ and $\sigma_R^0$. The correlations are in general good and the parameters of the regression equation reveal predominant control by the inductive effect. The influences of hydrogen bonding, steric inhibition of resonance, size of the substituent, and van der Waals forces are discussed. Carbon-13 chemical shifts for off-ring carbons in seven ortho-substituted aromatic systems have also been correlated with $\sigma_I$ and $\sigma_R^0$ but in only a few systems are the correlations good. Attempts to improve the correlations through removal of hydrogen-bonding substituents, variation of $\sigma_R^0$ for substituents with possible steric inhibition of resonance, and addition of van der Waals radii, the $Q$ parameter, and $\langle E^2 \rangle$ to the regression equation are discussed.

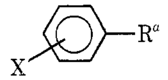
The analysis of the chemical and physical properties of ortho-substituted aromatics is potentially exceedingly complex. In addition to the conventional "through-the-ring" electronic effects, there is the possibility of interaction of the substituent with the ortho site through its electrical field, by van der Waals forces, hydrogen bonding, or dative bonding, or by steric inhibition of resonance as well as other steric effects, to mention just the more easily categorized effects and omitting, obviously, solvation effects. Consequently, it is not surprising that such systems have generally resisted analysis with the Hammett equation. While no one set of ortho-substituent constants has been found to be generally applicable, Charton has correlated reactivities and properties of many ortho-substituted systems with the divided substituent constants $\sigma_I$ and $\sigma_R^0$.[1]

The present study is an attempt to determine what substituent constants or other empirical parameters will correlate successfully with $^{13}C$ chemical shifts and $^{13}C$–$^1H$ coupling constants of off-ring carbons in ortho-substituted benzene derivatives. Since theoretical analyses of $^{13}C$–$^1H$ coupling constants point to a heavy dependence upon hybridization and effective nuclear charge,[2] it might be anticipated that correlations with inductive and resonance effects would be successful. Carbon-13 chemical shifts, however, appear to be sensitive to a greater number of factors, such as neighbor anisotropy effects, many of which are still poorly understood.[3]

## Experimental Section

**Compounds.** Most compounds were obtained commercially or prepared by standard procedures. Several, however, were previously unknown. Methyl *o*-fluorophenyl sulfide, bp 51–55 °C (1.7 mm) (Anal. Calcd for $C_7H_7FS$: C, 59.12; H, 4.97. Found: C, 59.26; H, 5.04), was prepared by methylation of the thiophenol with methyl iodide. *N,N*-Dimethyl-*o*-trifluoromethylaniline, bp 93 °C (17 mm) (Anal. Calcd for $C_9H_{10}F_3N$: C, 57.14; H, 5.33. Found: C, 56.85; H, 5.33), was obtained by methylation of *o*-trifluoromethylaniline

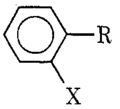
Table I. Coupling Constants, $J(^{13}C{-}Y)$ ± 0.3 Hz, for



| R | Y | X = H | F | Cl | Br | I | $CH_3$ | CN | $NO_2$ | $OCH_3$ | $NH_2$ | $N(CH_3)_2$ | $CF_3$ | $COCH_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $o$-$N(CH_3)_2$ | $^1H$ | 134.5 | 135.5 | 135.8 | | | 134.1 | | 136.3 | 134.3 | 134.2 | 134.3 | | |
| $o$-$COCH_3$ | $^1H$ | 127.2 | 128.4 | 128.4 | | | | | 128.8 | 128.0 | 127.1 | | | |
| $o$-$SCH_3$ | $^1H$ | 139.2 | 139.9 | 139.8 | 139.4 | | 139.0 | 140.8 | | 139.1 | | 138.9 | | |
| $o$-$CH_2Cl$ | $^1H$ | 150.3 | 152.7 | 152.1 | | | 150.5 | | 155.4 | 153.1 | | | | |
| $p$-$COCH_3$ | $^1H$ | 127.2 | 128.4 | 128.2 | | | | | 128.8 | 128.0 | 127.1 | | | |
| 2,6-$(CH_3)_2$ | $^1H$ | 125.6 | | | 127.7 | 127.65 | 125.5 | 127.6 | 128.7 | 126.75 | 125.5 | 126.4 | | |
| $o$-$CF_3$ | $^{19}F$ | 271.7 | | 274.0 | | 273.7 | | 273.7 | 272.9 | | 271.8 | 273.6 | | 272.8 |

[a] 30% in $CCl_4$.

Table II. Correlations of $(J_X - J_H)$ with $\sigma_I, \sigma_R{}^0$ for



| R | $J$ | $\rho_I$ | $\rho_R$ | $\lambda$ | $C$ | $r$ | $S_{est}$ | $F_{est}$ | C.L., % | $n$ |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | $^{13}C{-}^1H$ | 4.65 | 0.45 | 0.10 | 0.08 | 0.947 | 0.44 | 34.4 | 99.9 | 11 |
| $OCH_3$ | $^{13}C{-}^1H$ | 2.90 | 1.15 | 0.40 | 0.19 | 0.975 | 0.20 | 58.5 | 99.9 | 9 |
| $SCH_3$ | $^{13}C{-}^1H$ | 1.95 | 1.35 | 0.69 | 0.06 | 0.933 | 0.27 | 16.7 | 99 | 8 |
| $CH_2Cl$ | $^{13}C{-}^1H$ | 5.87 | 0.94 | 0.16 | 0.40 | 0.885 | 1.13 | 5.4 | 90 | 6 |
| $N(CH_3)_2$ | $^{13}C{-}^1H$ | 2.80 | 1.04 | 0.37 | −0.07 | 0.963 | 0.27 | 32.3 | 99.75 | 8 |
| CHO | $^{13}C{-}^1H$ | 22.86 | 9.50 | 0.42 | 0.40 | 0.975 | 1.72 | 48.7 | 99.9 | 8 |
| $COCH_3$ | $^{13}C{-}^1H$ | 2.58 | 0.20 | 0.08 | −0.06 | 0.968 | 0.22 | 22.5 | 97.5 | 6 |
| $Sn(CH_3)_3$ | $^{13}C{-}^1H$ | 1.81 | 1.28 | 0.71 | −0.13 | 0.958 | 0.19 | 22.1 | 99 | 7 |
| $CF_3$ | $^{13}C{-}^{19}F$ | 3.02 | −1.48 | −0.49 | 0.20 | 0.677 | 0.77 | 2.1 | 75 | 8 |
| $NH_2$ | $^{15}N{-}^1H$ | 12.65 | 9.96 | 0.79 | 0.01 | 0.931 | 2.04 | 9.7 | 95 | 6 |
| $Sn(CH_3)_3$ | $^{119}Sn{-}^{13}C$ | 34.48 | −5.05 | −0.15 | 0.28 | 0.957 | 3.03 | 21.8 | 99 | 7 |

with trimethyl phosphate. The preparations of the aryltrimethyltin derivatives were described previously.[4]

Solvents were spectroquality. Chloroform was shaken with alumina to remove ethanol.

**Coupling Constants.** Carbon-13–proton coupling constants were obtained from the proton satellites on a Varian A-60D NMR spectrometer with the standard sidebanding technique (Hewlett-Packard Model 200CD audiooscillator and 522B electronic counter). Carbon-13–fluorine coupling constants were obtained from $^{13}C$ spectra.

**Chemical Shifts.** Natural abundance $^{13}C$ NMR spectra were recorded on two spectrometers, both operating in the pulsed Fourier transform mode: (1) a modified Varian HA-100D spectrometer, operating at 25.14 MHz, equipped with a Digilab pulse and data system (FTS/NMR-3), described elsewhere,[5] and (2) a Varian XL-100-15 spectrometer operating at 25.21 MHz, equipped with a Varian 620-f computer and data system. Samples run on the XL-100 were contained in 12-mm o.d. tubes, with chloroform-$d$ serving as solvent and field-frequency lock material. Compounds studied using the modified HA-100D spectrometer were contained in 8-mm o.d. tubes which held coaxial inner cells containing $C_6F_6$, the $^{19}F$ lock substance.

Pseudorandom proton noise decoupling was employed with both spectrometers. All FT spectra were 8K or 16K transforms over spectral widths of 5000 Hz. Ambient probe temperature for both spectrometers was 39 °C.

Carbon chemical shifts were measured in parts per million relative to 5% internal $Me_4Si$. Positive values are deshielded relative to $Me_4Si$. Spectra used to obtain both $^{13}C{-}^1H$ coupling constants and $^{13}C$ chemical shifts were obtained from 30% solutions (v/v for liquids, w/v for solids) in either carbon tetrachloride or chloroform.

Assignments of carbon resonances were based on proton undecoupled spectra, additivity relationships, and literature values. Though not reported here, assignments were made for all ring carbons and these chemical shift values may be obtained from the authors.

**Regression Analyses.** Multiple linear regression analyses were accomplished with the stepwise Biomedical computer program BMD02R.[6] In all cases the dependent variable was the difference between the value (either chemical shifts or coupling constants) for the substituted derivative and that of the parent unsubstituted aromatic. All statistical measures of fit except confidence levels were a portion of the output of the program.

## Results and Discussion

**Coupling Constants.** Carbon-13 proton coupling constants for ortho-substituted toluenes, anisoles, benzaldehydes,[7] and trimethylphenylstannanes[8] have been reported previously. Coupling constants for ortho-substituted $N,N$-dimethylanilines, acetophenones, methyl phenyl sulfides, and benzyl chlorides are given in Table I. The coupling constant for the parent compound in each series was subtracted from the values for all members of the series and these substituent-induced values $(J_X{-}J_H)$ were then correlated with Taft's $\sigma_I$, $\sigma_R{}^0$ values[9] by multiple linear regression. Table II contains the parameters for the regression equation

$$J_X{-}J_H = \rho_I\sigma_I + \rho_R\sigma_R{}^0 + C \qquad (1)$$

where $\rho_I$ and $\rho_R$ express the dependence upon the substituent constants and $C$ is the intercept of the $\sigma_I$, $\sigma_R{}^0$ plane with the $J_X{-}J_H$ axis. The other parameters given in the table include $n$, the number of substituents correlated; $\lambda$, the ratio of $\rho_R$ to $\rho_I$ (see below); $r$, the multiple correlation coefficient; $S_{est}$, the standard deviation of the residuals; $F_{est}$, the $F$ level of the correlation; and C.L., the confidence level derived from $F_{est}$ for the significance of the correlation.[10] An attempt was made to include a basis set of substituents in each correlation and Taft's[9] definition of basis set was adopted for this purpose.

An examination of the confidence levels given in Table II reveals that all but one of the $^{13}C{-}^1H$ correlations are significant above the 95% confidence level. The use of the $F$ and $R$ values of Swain and Lupton[11] instead of $\sigma_I$ and $\sigma_R{}^0$ improved the correlations very slightly in a few cases but yielded slightly poorer correlations in others. The use of other resonance parameters,[9] such as $\sigma_{R(BA)}$, $\sigma_R{}^+$, and $\sigma_R{}^-$, led to improved correlations in some cases. For the toluenes, correlations with $\sigma_I$ and the following $\sigma_R$ parameters gave the $F$ levels: $\sigma_R{}^0$, 34.4; $\sigma_{R(BA)}$, 35.6; $\sigma_R{}^+$, 34.8; $\sigma_R{}^-$, 37.0. For the benzaldehydes: $\sigma_R{}^0$, 48.7; $\sigma_{R(BA)}$, 51.2; $\sigma_R{}^+$, 43.1; $\sigma_R{}^-$, 54.5. For the anisoles: $\sigma_R{}^0$, 58.5; $\sigma_{R(BA)}$, 38.0; $\sigma_R{}^+$, 28.0; $\sigma_R{}^-$, 91.0. Thus, for these systems $\sigma_R{}^-$ gave slightly better correlations for two and an appreciably better correlation for the third. However, because of the heavy weighting of NMR data in the definition of $\sigma_R{}^0$,[9] this measure of the resonance effect was used for all correlations.

Clearly, $^{13}$C–$^1$H coupling constants in ortho-substituted aromatics can be adequately described in terms of $\sigma_I$ and $\sigma_R{}^0$. As illustrated by the $^{15}$N–$^1$H and $^{119}$Sn–$^{13}$C coupling correlations given in Table II [$^{15}$N–$^1$H data (in $CHCl_3$) taken from Axenrod and Wieder;[12] $^{119}$Sn–$^{13}$C data from Schaeffer and Zuckerman[8]] other couplings are apparently also well described by these parameters. This is not the case for the $^{13}$C–$^{19}$F couplings, however. The correlation here is significant at only the 75% confidence level. Schuster reports an excellent correlation ($r = 1.000$) of four trifluorotoluene couplings with $\sigma_I$ and $\sigma_R{}^+$ but notes that substituents with a −R resonance effect (e.g., $NH_2$, NHAc, and OH) lead to deviations from the regression line.[13] The discrepancy is probably due to the presence of different substituents in the sets used for the correlations. Removal of the amino derivative from our set increased the significance of the correlation to the 95% confidence level ($\rho_I = 2.88$, $\rho_R = -2.68$, $\lambda = -0.93$, $r = 0.888$, $S_{est} = 0.45$, $F_{est} = 7.5$, $n = 7$).

In an attempt to determine the effect of hydrogen bonding on the significance of the correlations, the value for the amino derivative was removed from the anisole, benzaldehyde, acetophenone, and dimethylaniline sets. After removal of this value the $F$ values and confidence levels are, for anisoles, 145.9, 99.9%; benzaldehydes, 41.9, 99.75%; acetophenones, 44.1, 97.5%; dimethylanilines, 23.4, 99%. Thus, removal of the value for the amino derivative resulted in an improved correlation for the anisoles and acetophenones. Whether the lack of improvement for the other series is a result of an insensitivity of the coupling constant to hydrogen bonding, conformational obstruction to hydrogen bonding (for example, ortho-substituted acetophenones have the carbonyl oriented toward the ortho substituent,[14] whereas the favored conformation for many ortho benzaldehydes has the oxygen away from the substituent[15]), or some other characteristic of these systems that results in a good fit for the $NH_2$ derivative is not clear.

The effect of steric inhibition of resonance on $N$-alkyl $^{13}$C–$^1$H coupling constants in 2- and 2,6-disubstituted $N$-alkylanilines has been reported.[16] The abstraction of an effect due to steric inhibition of resonance with multiple regression analysis is not as straightforward. The dimethylanilines might be expected to yield poor correlations with $\sigma_I$ and $\sigma_R{}^0$ because of steric inhibition of conjugation of the amino nitrogen with the benzene ring. However, for some substituents (e.g., $NO_2$), steric inhibition of resonance of the substituent induced by the dimethylamino group is also possible, and conjugation of the substituent and the ortho site with the ring is not independent. In any event, the correlation with $\sigma_I$ and $\sigma_R{}^0$ for the dimethylanilines is quite good.

The toluenes present a system in which conjugation of only the substituent can be sterically inhibited. In order to test the sensitivity of the correlation to this phenomenon, correlations were performed with $\sigma_R{}^0$ values for the dimethylamino substituent ranging from −0.52 to 0.00. The resultant $F$ levels ranged: $\sigma_R{}^0 = -0.52$, $F = 34.4$; $\sigma_R{}^0 = -0.35$, $F = 36.7$; $\sigma_R{}^0 = -0.25$, $F = 38.4$; $\sigma_R{}^0 = 0.00$, $F = 42.5$. Thus, a decrease in the resonance contribution (electron release) of the dimethylamino group does result in an increase in the significance of the correlation.

Correlations were also performed for the 2,6-dimethyl series (Table I). With substituents for which steric inhibition of resonance should be minimal (Br, I, CN, $NH_2$, H, $CH_3$) the correlation is significant at the 95% level ($F_{est} = 13.4$, $r = 0.948$) and the ratio of the $\rho_R$ to $\rho_I$ is low ($\rho_I = 4.28$, $\rho_R = 0.41$, $\lambda = 0.096$). The addition of the nitro, methoxy, or dimethylamino substituent to this set increases the significance of the correlation, although the correlation coefficient is lower for methoxy ($r = 0.947$) and dimethylamino ($r = 0.925$). A decrease in $\sigma_R{}^0$ for $N(CH_3)_2$ to 0.0 increases the $F$ level slightly from 11.8 to 13.3. When all of the substituents are included, the correlation is significant at the 99.75% confidence level ($F_{est} = 26.6$, $r = 0.948$) and the ratio of $\rho_R$ to $\rho_I$ is even lower ($\rho_I = 4.40$, $\rho_R = -0.07$, $\lambda = -0.016$). Thus, the strong dependence on $\sigma_I$ renders the correlations relatively insensitive to steric inhibition of resonance even in the 2,6-dimethyl system.

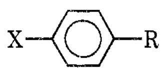
**Addition of Other Variables.** The possibility that the addition of other variables to the regression equation would improve the correlation of coupling constants was tested with three variables: $V$, the van der Waals radius; $Q$, the parameter defined by Hruska, Hutton, and Schaefer[17] and believed to be related to the paramagnetic term in Ramsey's equation[18,19] (and important, therefore, mainly in chemical shifts, see below); and $\langle E^2 \rangle$, presumably a measure of intramolecular dispersion forces (see below). The addition of the third variable was judged to be significant when the confidence level for addition was equal to or greater than 95% as determined by the sequential $F$ test.[10] The correlations with $\sigma_I$, $\sigma_R{}^0$, and $V$ were performed on the toluenes, anisoles, and benzaldehydes using Bondi's[20] van der Waals radii for the substituents F, Cl, Br, I, H, and O (radii of $OCH_3$ assumed to be that of oxygen)[21] and Charton's[21] $V_{max}$ and $V_{min}$ for the $CH_3$ and $NO_2$ groups. The correlations of coupling constants with $\sigma_I$, $\sigma_R{}^0$, and Q were run for all systems given in Table II, and correlations with $\sigma_I$, $\sigma_R{}^0$, and $\langle E^2 \rangle$ were performed for the toluenes and benzaldehydes. The calculations of values of $Q$ and $\langle E^2 \rangle$ are discussed below.

Using the $F_{add}$ criteria for significance, only the $\sigma_I$, $\sigma_R{}^0$, $V$ correlation (using either $V_{max}$ or $V_{min}$ for $NO_2$ and $CH_3$) for the anisoles (with $V_{max}$, $n = 8$, $F_{est} = 274$, $F_{add} = 9.9$, confidence level for addition = 95%) and the $\sigma_I$, $\sigma_R{}^0$, $Q$ correlation for the toluenes ($n = 11$, $F_{est} = 45.9$, $F_{add} = 8.1$, confidence level for addition = 97.5%) were significant. Hence, it appears that *in general* $V$, $Q$, and $\langle E^2 \rangle$ are not significant determinants of variations in ortho coupling constants.

**Composition of Electronic Effect.** Coupling constants in ortho aromatics are apparently determined, therefore, by inductive and resonance effects. The relative composition of this electronic effect can be expressed in terms of $\lambda$, the ratio of $\rho_R$ to $\rho_I$. The $\lambda$ values reported in Table II are all less than 1.0, indicating a predominance of the inductive effect for all systems studied. With few exceptions, the lowest values of $\lambda$ for $^{13}$C–$^1$H couplings appear in those systems that contain the C–H bond directly attached to the ring, e.g., the toluenes and benzyl chlorides. In systems like the anisoles, methyl phenyl sulfides, dimethylanilines, and trimethylphenylstannanes, the methyl group is further removed from the ring, the inductive effect is correspondingly attenuated, and $\lambda$ is therefore higher. The benzaldehydes and acetophenones are apparently exceptions to these generalizations. In the benzaldehydes, the hydrogen is attached to a carbon capable of conjugation with the ring and $\lambda$ is, therefore, higher than in the toluenes. The low value for the acetophenones is not easily rationalized.

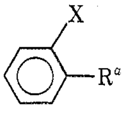
In order to compare the composition of the ortho electronic effect (as manifested by $^{13}$C–$^1$H coupling constants) to that of the para electronic effect, coupling constant data

Table III. Correlations of ($J_X$–$J_H$) with $\sigma_I$, $\sigma_R{}^0$ for



| R | J | $\rho_I$ | $\rho_R$ | λ | C | r | $S_{est}$ | $F_{est}$ | C.L., % | n |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | $^{13}C$–$^1H$ | 1.94 | 1.30 | 0.67 | −0.03 | 0.996 | 0.062 | 258.7 | 99.9 | 7 |
| $OCH_3$ | $^{13}C$–$^1H$ | 1.73 | 2.25 | 1.30 | 0.09 | 0.977 | 0.188 | 74.3 | 99.9 | 10 |
| CHO | $^{13}C$–$^1H$ | 7.59 | 9.29 | 1.22 | −0.70 | 0.978 | 0.823 | 64.4 | 99.9 | 9 |
| $COCH_3$ | $^{13}C$–$^1H$ | 0.86 | 1.55 | 1.80 | 0.12 | 0.957 | 0.153 | 27.4 | 99.75 | 8 |
| $CF_3$ | $^{13}C$–$^{19}F$ | 1.67 | 3.19 | 1.91 | −0.33 | 0.970 | 0.344 | 39.9 | 99.9 | 8 |
| $NH_2$ | $^{15}N$–$^1H$ | 8.43 | 13.33 | 1.58 | −0.06 | 0.992 | 0.493 | 151.8 | 99.9 | 8 |
| $Sn(CH_3)_3$ | $^{119}Sn$–$^{13}C$ | 15.10 | 9.08 | 0.60 | 0.37 | 0.987 | 0.702 | 74.8 | 99.9 | 7 |

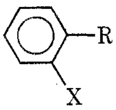
Table IV. $^{13}C$ Chemical Shifts (±0.05 ppm) for Off-Ring Carbons of



| R | X = H | F | Cl | Br | I | $CH_3$ | CN | $NO_2$ | $COCH_3$ | $OCH_3$ | $NH_2$ | $N(CH_3)_2$ | $CF_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | 21.42 | 14.36 | 19.98 | 22.84 | 28.04 | 19.66 | 20.35 | 20.25 | | 16.23 | 17.17 | 18.33 | |
| $OCH_3$ | 54.99 | 56.03 | 55.87 | 55.99 | 56.16 | 54.98 | | 56.52 | 55.48 | 55.73 | 55.36 | | |
| CHO | 192.33 | 187.15 | 189.47 | 191.34 | | 192.61 | | 188.33 | | 189.49 | 194.13 | | |
| $N(CH_3)_2$ | 40.30 | | | 44.01 | | 44.22 | | 42.12 | | 43.06 | | 41.39 | 45.63 |
| $CF_3$ | 124.62 | | 122.77 | | 122.84 | | 122.14 | 122.07 | 123.50 | | 125.18 | 124.33 | |

[a] 30% in $CDCl_3$.

Table V. Correlations of ($\delta_X$–$\delta_H$) with $\sigma_I$, $\sigma_R{}^0$ for



| R | δ | $\rho_I$ | $\rho_R$ | C | r | $S_{est}$ | $F_{est}$ | C.L., % | n |
|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | $^{13}C$ | −1.44 | 7.69 | 0.44 | 0.465 | 3.59 | 1.1 | 50 | 11 |
| $OCH_3$ | $^{13}C$ | 2.18 | −0.13 | 0.03 | 0.966 | 0.15 | 48.3 | 99.9 | 10 |
| $N(CH_3)_2$ | $^{13}C$ | 2.24 | 0.34 | 2.12 | 0.347 | 2.10 | 0.3 | <50 | 7 |
| CHO | $^{13}C$ | −7.53 | −0.04 | 0.53 | 0.800 | 1.69 | 4.5 | 90 | 8 |
| $COCH_3$ | $^{13}CO$ | −1.86 | 3.03 | −1.72 | 0.453 | 1.59 | 0.65 | <50 | 8 |
| | $^{13}CH_3$ | −4.80 | 4.55 | −1.42 | 0.708 | 1.54 | 2.5 | 75 | 8 |
| $Sn(CH_3)_3$ | $^{13}C$ | 0.85 | 0.37 | 0.77 | 0.342 | 0.72 | 0.3 | <50 | 7 |
| $CF_3$ | $^{13}C$ | −4.22 | −0.63 | 0.06 | 0.955 | 0.41 | 25.7 | 99.75 | 8 |
| $NH_2$ | $^{15}N$ | 2.55 | 2.06 | −0.08 | 0.837 | 0.69 | 3.5 | 75 | 6 |
| $Sn(CH_3)_3$ | $^{119}Sn$ | 28.98 | 34.50 | 0.93 | 0.990 | 1.74 | 103.5 | >99.9 | 7 |

of para-substituted systems were also correlated via eq 1 to $\sigma_I$ and $\sigma_R{}^0$. Coupling constants for the toluenes,[22] anisoles,[22] and benzaldehydes[23] were reported previously; constants for the acetophenones are listed in Table I. Correlations for $^{13}C$–$^{19}F$,[14] $^{15}N$–$^1H$,[24] and $^{119}Sn$–$^{13}C$[8] couplings were also performed. The results of the correlations are given in Table III, from which it is obvious that (a) the correlations are excellent in general, and (b) λ is frequently greater than 1.0 and always higher than that for the ortho correlations. This latter conclusion is easily rationalized on the basis of an increased inductive effect resulting from the increased proximity of substituent and reaction site in the ortho derivatives and supports Charton's[1] conclusion that in general the composition of the ortho and para electronic effects are different.

**Chemical Shift Correlations.** The off-ring carbon chemical shifts reported in Table IV were correlated with $\sigma_I$ and $\sigma_R{}^0$ according to the equation

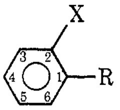
$$\delta_X - \delta_H = \rho_I\sigma_I + \rho_R\sigma_R{}^0 + C \qquad (2)$$

These correlations are tabulated in Table V. Also given there are correlations for $^{13}C$ shifts of ortho-substituted acetophenones,[25] trimethylphenylstannanes,[8] $^{15}N$ shifts for anilines (in $CDCl_3$),[12] and $^{119}Sn$ shifts for trimethylphenylstannanes.[4] For only three systems, the anisoles, trifluorotoluenes, and trimethylphenylstannanes, were the correlations significant above the 95% confidence level. Correlations with $\sigma_I$ and the other resonance parameters for the toluenes, anisoles, and benzaldehydes produced the following F levels: toluenes, $\sigma_{R(BA)}$, 1.5; $\sigma_R{}^-$, 0.95; $\sigma_R{}^+$, 1.2; anisoles, $\sigma_{R(BA)}$, 43.7; $\sigma_R{}^-$, 47.2; $\sigma_R{}^+$, 48.9; benzaldehydes, $\sigma_{R(BA)}$, 4.5; $\sigma_R{}^-$, 4.5; $\sigma_R{}^+$, 4.9. Thus, for the anisoles and benzaldehydes $\sigma_R{}^+$ led to a slight improvement in the correlations, while for the toluenes $\sigma_{R(BA)}$ provided the best correlation (though differences are small).

The F levels for the correlation of ($\delta_X$–$\delta_H$) for the ring carbons with $\sigma_I$ and $\sigma_R{}^0$ are presented in Table VI. The parameters of eq 2 are given in Table VII for those correlations significant at or above the 95% confidence level. As is apparent from the table, correlations for C(5) are consistently good, while shifts at C(4) and C(6) occasionally afford good correlations. The other ring carbons rarely exhibit good correlations. These trends and the predominance of the resonance effect at C(5), the carbon para to the X substituent, are consistent with previous observations.[26]

The possible influence of hydrogen bonding between the substituent and the reaction site was examined by removal of the amino group from the set of substituents for the ani-

Table VI. F Levels for Correlations of $^{13}C$ Ring Shifts with $\sigma_I$, $\sigma_R{}^0$ [a] and $\sigma_I$, $\sigma_R{}^0$, and $Q$ [b] for



| R | | C(1) | C(2) | C(3) | C(4) | C(5) | C(6) |
|---|---|---|---|---|---|---|---|
| $CH_3$ | $\sigma_I$, $\sigma_R{}^0$ | 3.4 | 1.2 | 2.1 | 24.3 | 18.2 | 3.5 |
| | $\sigma_I$, $\sigma_R{}^0$, $Q$ | 11.3 | 2.2 | 6.1 | 0.2 | 27.5 | 0.01 |
| $OCH_3$ | $\sigma_I$, $\sigma_R{}^0$ | 7.0 | 0.4 | 2.1 | 1.3 | 90.5 | 1.4 |
| | $\sigma_I$, $\sigma_R{}^0$, $Q$ | 6.8 | 7.1 | 6.0 | 11.4 | 4.0 | 3.8 |
| CHO | $\sigma_I$, $\sigma_R{}^0$ | 2.5 | 1.1 | 2.1 | 12.2 | 44.1 | 0.7 |
| | $\sigma_I$, $\sigma_R{}^0$, $Q$ | 5.2 | 18.5 | 13.5 | 0.5 | 1.1 | 0.002 |
| $CF_3$ | $\sigma_I$, $\sigma_R{}^0$ | 0.7 | 0.03 | 0.6 | 4.1 | 17.0 | 6.2 |
| | $\sigma_I$, $\sigma_R{}^0$, $Q$ | 0.4 | 0.1 | 0.7 | 1.6 | 1.9 | 6.5 |
| $N(CH_3)_2$ | $\sigma_I$, $\sigma_R{}^0$ | 1.1 | 0.5 | 1.8 | 0.2 | 85.2 | 0.4 |
| | $\sigma_I$, $\sigma_R{}^0$, $Q$ | 0.05 | 0.2 | 0.04 | 0.05 | 4.2 | 1.4 |
| $COCH_3$ | $\sigma_I$, $\sigma_R{}^0$ | 1.8 | 0.3 | 0.09 | 0.2 | 49.2 | 7.8 |
| | $\sigma_I$, $\sigma_R{}^0$, $Q$ | 18.1 | 84.8 | 1.2 | 0.4 | 12.8 | 0.25 |
| $Sn(CH_3)_3$ | $\sigma_I$, $\sigma_R{}^0$ | 1.3 | 8.8 | 3.0 | 36.9 | 3.9 | 5.4 |
| | $\sigma_I$, $\sigma_R{}^0$, $Q$ | 9.1 | 1.8 | 1.9 | 2.6 | 16.9 | 12.2 |

[a] $F_{est}$ for $\sigma_I$, $\sigma_R{}^0$ correlations. [b] $F_{add}$ for $\sigma_I$, $\sigma_R{}^0$, $Q$ correlations.

Table VII. Correlations of $(\delta_X - \delta_H)$ of Ring Carbons with $\sigma_I$, $\sigma_R{}^0$ Significant at or above the 95% Confidence Level

| R | Carbon | $\rho_I$ | $\rho_R$ | $C$ | $r$ | $S_{est}$ | $F_{est}$ | C.L., % | $n$ |
|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | C(4) | 2.44 | −1.97 | 0.16 | 0.927 | 0.27 | 24.3 | 99.9 | 11 |
| | C(5) | 2.17 | 17.73 | 0.35 | 0.906 | 2.16 | 18.2 | 99.75 | 11 |
| $OCH_3$ | C(1) | −7.67 | 16.15 | −0.42 | 0.816 | 3.07 | 7.0 | 97.5 | 10 |
| | C(5) | 5.34 | 20.96 | −0.25 | 0.981 | 1.11 | 90.5 | 99.9 | 10 |
| CHO | C(4) | 1.52 | −4.25 | −0.70 | 0.911 | 0.51 | 12.2 | 97.5 | 8 |
| | C(5) | 6.02 | 21.98 | −0.45 | 0.973 | 1.48 | 44.1 | 99.9 | 8 |
| $CF_3$ | C(5) | 4.29 | 16.51 | −0.19 | 0.934 | 2.36 | 17.0 | 99 | 8 |
| | C(6) | 3.51 | −2.32 | 0.13 | 0.844 | 0.54 | 6.2 | 95 | 8 |
| $N(CH_3)_2$ | C(5) | 3.18 | 15.81 | −0.36 | 0.989 | 0.84 | 85.2 | 99.9 | 7 |
| $COCH_3$ | C(5) | −6.03 | −21.13 | 0.48 | 0.976 | 1.34 | 49.2 | 99.9 | 8 |
| | C(6) | 4.75 | 3.92 | −0.89 | 0.870 | 1.06 | 7.8 | 97.5 | 8 |
| $Sn(CH_3)_3$ | C(2) | 10.80 | −52.03 | 0.09 | 0.903 | 7.06 | 8.8 | 95 | 7 |
| | C(4) | 2.21 | −2.99 | 0.00 | 0.974 | 0.25 | 36.9 | 99.5 | 7 |

soles, benzaldehydes, and acetophenones. Neither the off-ring or C(5) correlations were improved for the anisoles while both the formyl carbon and C(5) correlations improved (to the 95 and 99.9% confidence levels, respectively) for the benzaldehydes. Only the methyl correlation improved (to the 90% confidence level) for the acetophenones. Thus the relationship between intramolecular hydrogen bonding and the significance of these correlations is uncertain. Moreover, there is in general no parallel between the results obtained for the coupling constant and chemical shift correlations.

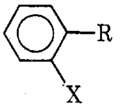
The effect of steric inhibition of resonance on $^{13}C$ shift correlations was tested by performing the correlation with $\sigma_I$ and $\sigma_R{}^0$ for the toluenes using values ranging from −0.52 to −0.25 for $\sigma_R{}^0$ for the dimethylamino group. A decrease in the absolute value of $\sigma_R{}^0$ resulted in a slight decrease in $F_{est}$, and thus there appears to be no evidence that steric inhibition of resonance of the $N(CH_3)$ substituent has resulted in deviation from the correlation plane for the toluenes.

**Addition of Other Variables.** The possibility of a relation between size of the ortho substituent and $^{13}C$ chemical shift at the reaction site was tested by addition of the variable $V$ (vide supra) to the regression equation. Correlations to $\sigma_I$, $\sigma_R{}^0$, and $V$ were run for the toluenes, anisoles, and benzaldehydes. When either $V_{min}$ or $V_{max}$ was used for $CH_3$ and $NO_2$ the addition of $V$ for the off-ring carbons was not significant at the 95% confidence level. For the ring carbons, the addition of $V$ was significant at this level for C(6) of the anisoles and C(4) of the benzaldehydes using $V_{max}$ for $-CH_3$ and $-NO_2$, and C(4) of the toluenes, C(6) of the anisoles, and C(4) of the benzaldehydes using $V_{min}$ for $-CH_3$ and $-NO_2$. *In general*, then, the addition of $V$ to the regression equation is not justified.

The $Q$ parameter, defined by Hruska, Hutton, and Schaefer[17] as $P/Ir^3$, where $P$ is the polarizability of the C–X bond of the ortho substituent, $I$ is the first ionization potential of the X atom, and $r$ is the C–X bond length, has been applied with some success to proton,[17,27–30] fluorine,[17,27] and carbon[30] shifts in ortho or cis configurations. The parameter has been related to the paramagnetic term in the Ramsey equation.[17] The $F$ levels for the addition of $Q$ to eq 2 for the ring carbons are given in Table VI. The $Q$ values were taken from the compilation of values for ortho substituents based on the proton shifts in various halobenzenes.[29] The $Q$ value for the $N(CH_3)_2$ group was calculated from a least-squares plot of the C(3) proton chemical shifts of 2-substituted chlorobenzenes vs. the $Q$ value of the substituents. The proton shift for 2-dimethylaminochlorobenzene was taken from the work of Goetz, Nerdel, and Rehsc.[31]

The $F_{add}$ values reported in Table VI are significant at the 95% confidence level for the following carbons: toluenes, C(1), C(3), C(5); anisoles, C(1), C(2), C(3), C(4); benzaldehydes, C(2), C(3); trifluorotoluenes, none; dimethylanilines, none; acetophenones, C(1), C(2), C(5); trimethylphenylstannanes, C(5), C(6). Hence, in three out of the seven systems studied the addition of $Q$ is significant at the 95% confidence level (in five out of seven the addition is significant at the 90% confidence level) for the carbon ortho to the substituent and attached to the reaction site, that is, C(1). In three out of seven systems the addition is

Table VIII. Three Parameter ($\sigma_I$,$\sigma_R{}^0$, $P$) Correlations of ($\delta_X - \delta_H$) for Off-Ring Carbons of



| R | $P$ | $\rho_I$ | $\rho_R$ | $\rho_P$ | $C$ | $r$ | $S_{est}$ | $F_{est}$ | $F_{add}$ | C.L.$_{add}$ | $n$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | $Q$ | −4.84 | −1.04 | 2.55 | −6.11 | 0.805 | 2.57 | 4.3 | 8.6 | 97.5 | 11 |
| $CH_3$ | $\langle E^2 \rangle$ | −4.66 | 15.84 | 1.45 | −1.72 | 0.954 | 1.53 | 17.0 | 30.0 | 99.5 | 9 |
| CHO | $\langle E^2 \rangle$ | −12.06 | −0.01 | 0.83 | −1.16 | 0.986 | 0.56 | 35.0 | 41.1 | 99 | 7 |

significant at the 95% level for the carbon bearing the substituent. In three out of seven systems the addition is significant at the 95% level for the other carbon, C(3), ortho to the substituent. The addition of $Q$ to the regression equation is, therefore, significant for ortho carbons and those attached to the substituent in some cases but certainly not in all. For most correlations for which $F_{add}$ is significant at the 95% level the overall correlation is also significant at that level. The correlations for C(2) and C(3) of the anisoles were significant at lower confidence levels.

Correlations of the off-ring carbons with $\sigma_I$, $\sigma_R{}^0$, and $Q$ were also performed. For only one system, the toluenes, was the addition of $Q$ significant at the 95% confidence level. The parameters of this overall poor correlation are given in Table VIII.

Another parameter used to correlate proton,[32] fluorine,[33–35] and carbon[32] chemical shifts is the nonzero time average electric field, $\langle E^2 \rangle$, generated by time dependent dipole moments in neighboring substituents. These van der Waals forces can be estimated by the equation[33,36]

$$\langle E^2 \rangle = \frac{3PI}{r^6} \quad (3)$$

where $P$ is the polarizability of the substituent, $I$ is the first ionization potential, and $r$ is the distance between the reaction site and the substituent. In calculating values of $\langle E^2 \rangle$ we have assumed $P$ to be the polarizability of the bond from the ring to the first atom of the substituent and the bond refractivities given by Smythe[37] were converted to polarizabilities. The ionization potential was assumed to be that of the first atom of the substituent (e.g., O of $OCH_3$), and $r$ was defined as the distance from a carbon of the ortho site to the center of the bond from the ring to the first atom of the substituent. The distance $r$ was calculated using simple geometry, bond lengths from model compounds,[38] and an angle of 120° for all ring-substituent angles. For the anisoles, $r$ was calculated for two conformations: in one the methyl group is coplanar with the ring and oriented away from the ortho substituent; in the other the methyl group is in a plane perpendicular to the ring. For the acetophenones, the configuration reported by Montaudo et al.[14] was assumed to be constant throughout the series. The distance $r$ for the trimethylphenylstannanes was calculated for the methyl carbon in four conformations. In one, a reflection of the methyl group on the tin-phenyl axis was used as an average position. In a second conformation, the methyl group was assumed to be in the plane of the ring and away from the ortho substituent, while in the third case it was oriented toward the substituent. In the fourth conformation, one methyl group is in the plane of the ring and away from the substituent and $r$ is calculated to one of the other methyl groups (toward the substituent) in that conformation.

The off-ring $^{13}C$ and $^{119}Sn$ shifts were then correlated to $\sigma_I$, $\sigma_R{}^0$, and $\langle E^2 \rangle$ for the toluenes, benzaldehydes, acetophenones, anisoles (two correlations, one for each conformation), trimethylphenylstannanes (five correlations: four conformations for $^{13}C$, one for $^{119}Sn$). Of these, only two, the toluenes and benzaldehydes, resulted in a value for $F_{add}$ at or above the 95% confidence level. As is obvious from Table VIII, these correlations are quite good and the addition of $\langle E^2 \rangle$ clearly resulted in a significant improvement.

It appears then that none of the three parameter linear equations employed above can provide satisfactory correlations for a majority of the systems studied. However, the electronic, "paramagnetic", and dispersion effects are not the only factors capable of influencing chemical shifts. A recent review[39] includes, in addition to the factors discussed above, the neighbor anisotropy, steric polarization, electric field, and solvent effects.

While the shielding due to the magnetic field produced by an ortho substituent can be calculated using the point-dipole approximation,[40] the necessary magnetic susceptibilities for the substituents are not accurately known. Moreover, the point-dipole approximation is valid only when the distance between the substituent and the reaction site is greater than the size of the bond or group producing the magnetic field.

The steric polarization effect has been placed on a quantitative basis for gauche 1-4 carbon atoms,[41] but not for the interaction of a carbon atom with a heteroatom in the $\gamma$ position (some of which have recently been ascribed to hyperconjugative interactions[42]).

The effect of an electric field generated by a polar substituent on a chemical shift at the reaction site can be described by the Buckingham equation[43] and involves two terms, one dependent upon the component of the electric field along the bond direction at the reaction site, the other dependent upon the square of the electric field.

$$\Delta\sigma = -AE_Z - BE^2 \quad (4)$$

Feeney, Sutcliffe, and Walker[32] have assumed that the changes in $^{13}C$ chemical shifts due to changes in $E_Z$ and $E^2$ are negligible in a series of halogenated ethanes, owing presumably to the similarity in the magnitudes of the bond dipole moment of the C–X bonds, coupled with the compensating effect of the distance from substituent to the $^{13}C$ nucleus and the magnitudes of the constants $A$ and $B$. Carbon-13 shifts in some systems have been rationalized, however, in terms of the electric field model.[39]

The effect of solvent has also not been taken into account. Chloroform is known to produce shifts relative to solvents like $CCl_4$ or cyclohexane, especially for compounds capable of acceptor hydrogen bonding.[3] The magnitude of these solvent interactions and their variations with substituent is at present impossible to predict.

Thus, it is possible that more accurate quantization of factors such as neighbor anisotropy, solvent effects, etc., will yield improved correlations and understanding of ortho $^{13}C$ shifts. It seems likely, however, that the $^{13}C$ shifts of ortho derivatives must be described in terms of a complex mix of factors, the composition of which may vary from substituent to substituent and from system to system.

Carbon-13–proton (and other) couplings, on the other hand, can be described with fair success in terms of only the inductive and resonance substituent parameters.

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**Registry No.**—*N*,*N*-Dimethylaniline, 121-69-7; *o*-fluoro-*N*,*N*-dimethylaniline, 393-56-6; *o*-chloro-*N*,*N*-dimethylaniline, 698-01-1; *N*,*N*,*o*-trimethylaniline, 609-72-3; *N*,*N*-dimethyl-*o*-nitroaniline, 610-17-3; *o*-methoxy-*N*,*N*-dimethylaniline, 700-75-4; *N*,*N*-dimethyl-1,2-benzenediamine, 2836-03-5; *N*,*N*,*N*′,*N*′-tetramethyl-1,2-benzenediamine, 704-01-8; acetophenone, 98-86-2; *o*-fluoroacetophenone, 445-27-2; *o*-chloroacetophenone, 2142-68-9; *o*-nitroacetophenone, 577-59-3; *o*-methoxyacetophenone, 579-74-8; *o*-aminoacetophenone, 551-93-9; methyl phenyl sulfide, 100-68-5; methyl *o*-fluorophenyl sulfide, 655-20-9; methyl *o*-chlorophenyl sulfide, 17733-22-1; methyl *o*-bromophenyl sulfide, 19614-16-5; methyl *o*-tolylsulfide, 14092-00-3; methyl *o*-cyanophenyl sulfide, 6609-54-7; methyl *o*-methoxyphenyl sulfide, 2388-73-0; methyl *o*-(dimethylamino)phenyl sulfide, 2388-50-3; benzyl chloride, 100-44-7; *o*-fluorobenzyl chloride, 345-35-7; *o*-chlorobenzyl chloride, 611-19-8; *o*-methylbenzyl chloride, 552-45-4; *o*-nitrobenzyl chloride, 612-23-7; *o*-methoxybenzyl chloride, 7035-02-1; *p*-fluoroacetophenone, 403-42-9; *p*-chloroacetophenone, 99-91-2; *p*-nitroacetophenone, 100-19-6; *p*-methoxyacetophenone, 100-06-1; *p*-aminoacetophenone, 99-92-3; 2,6-dimethylbenzene, 108-38-3; 1-bromo-2,6-dimethylbenzene, 576-22-7; 1-iodo-2,6-dimethylbenzene, 608-28-6; 1,2,6-trimethylbenzene, 526-73-8; 1-cyano-2,6-dimethylbenzene, 6575-13-9; 1-nitro-2,6-dimethylbenzene, 81-20-9; 1-methoxy-2,6-dimethylbenzene, 1004-66-6; 2,6-dimethylaniline, 87-62-7; *N*,*N*,2,6-tetramethylaniline, 769-06-2; (trifluoromethyl)benzene, 98-08-8; 1-chloro-2-(trifluoromethyl)benzene, 88-16-4; 1-iodo-2-(trifluoromethyl)benzene, 444-29-1; 1-cyano-2-(trifluoromethyl)benzene, 447-60-9; 1-nitro-2-(trifluoromethyl)benzene, 384-22-5; 2-(trifluoromethyl)aniline, 88-17-5; *N*,*N*-dimethyl-*o*-(trifluoromethyl)aniline, 54672-14-9; *o*-(trifluoromethyl)acetophenone, 17408-14-9; toluene, 108-88-3; *o*-fluorotoluene, 95-52-3; *o*-chlorotoluene, 95-49-8; *o*-bromotoluene, 95-46-5; *o*-iodotoluene, 615-37-2; 1,2-dimethylbenzene, 95-47-6; *o*-methylbenzonitrile, 529-19-1; *o*-nitrotoluene, 88-72-2; *o*-methoxytoluene, 578-58-5; *o*-toluidine, 95-53-4; *N*,*N*-dimethyl-*o*-toluidine, 609-72-3; anisole, 100-66-3; *o*-fluoroanisole, 321-28-8; *o*-chloroanisole, 766-51-8; *o*-bromoanisole, 578-57-4; *o*-iodoanisole, 529-28-2; *o*-nitroanisole, 91-23-6; 1,2-dimethoxybenzene, 91-16-7; *o*-methoxyaniline, 90-04-0; benzaldehyde, 100-52-7; *o*-fluorobenzaldehyde, 446-52-6; *o*-chlorobenzaldehyde, 89-98-5; *o*-bromobenzaldehyde, 6630-33-7; *o*-methylbenzaldehyde, 529-20-4; *o*-nitrobenzaldehyde, 552-89-6; *o*-methoxybenzaldehyde, 135-02-4; *o*-aminobenzaldehyde, 529-23-7; *o*-bromo-*N*,*N*-dimethylaniline, 698-00-0; thiophenol, 108-98-5; methyl iodide, 74-88-4; trimethyl phosphate, 512-56-1.

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