volume of 10 mL. The mixture was stirred for 1 h, and the dark red product was extracted into chloroform. After removal of chloroform on a rotary evaporator, a dark red solid was obtained. Spectral data of 8 were obtained (Results) immediately upon isolation, since this compound is quite sensitive to air oxidation to the 1-isoquinolinone. Upon evaporation to dryness of the aqueous layer from the above extraction, a solid was obtained which had a ^{1}H NMR spectrum in D_2O [δ 6.02 (2 H, s), 7.60 (5 H, s), 8.33 (1 H, quasi triplet), 9.02 (1 H, d), 9.18 (1 H, d), 9.45 (1 H, s)] identical with that of the 1-benzylnicotinamide cation.

Product isolation from the reduction of **7** by either 1-(4-cyanobenzyl)-1,4-dihydronicotinamide or 1-benzyl-4,4-dideuterio-1,4-dihydronicotinamide was done in a similar manner, except that 5- and 3-fold excesses, respectively, of the isoquinolinium salt were used to speed up the reaction.

Kinetic Studies. All rate data were obtained in 20% acetonitrile–80% water (v/v) at 25 °C, pH 7.0 (0.005 M phosphate buffer), and an ionic strength of 1.0 (KCl). The absorbance at 450 nm was recorded as a function of time with either a Unicam SP-1800 spectrophotometer equipped with a Unicam AR-25 linear recorder or with a Varian Cary 210 spectrophotometer. Reaction solutions contained the 1,4-dihydronicotinamide (0.08 mM) and appropriate concentrations of the isoquinolinium cation (1–50 mM) in a 10 mm path length cell.

Pseudo-first-order rate constants were evaluated from the slopes of Guggenheim plots over 2–4 reaction half-times after digitizing the absorbance vs. time curves by using the interactive digital plotter of a Tektronix 4051 computer.

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Registry No. 1 (X = 4-CH_3), 56133-29-0; 1 (X = H), 952-92-1; 1 (X = 4-F), 1893-57-8; 1 (X = 4-Br), 78186-16-0; 1 (X = 3-F), 78186-17-1; 1 (X = 4-CF_3), 78186-18-2; 1 (X = 3-CN), 78186-19-3; 1 (X = 4-CN), 56133-27-8; 2 (Z = 4-CH_3), 64840-46-6; 2 (Z = H), 52166-52-6; 2 (Z = 4-F), 78186-20-6; 2 (Z = 4-Br), 64840-44-4; 2 (Z = 3-F), 64840-45-5; 2 (Z = 4-CF_3), 78186-21-7; 2 (Z = 3-CN), 64840-43-3; 2 (Z = 4-CN), 64840-42-2; 3 (X = 4-CH_3), 78186-22-8; 3 (X = H), 16183-83-8; 3 (X = 4-F), 78186-23-9; 3 (X = 4-Br), 78186-24-0; 3 (X = 3-F), 78186-25-1; 3 (X = 4-CF_3), 78186-26-2; 3 (X = 3-CN), 78186-27-3; 3 (X = 4-CN), 78186-28-4; 7, 46271-32-3; 8, 69337-15-1; 9, 17750-24-2; 10, 60172-94-3; nicotinamide, 98-92-0; 4-methylbenzyl bromide, 104-81-4; benzyl bromide, 100-39-0; 4-fluorobenzyl bromide, 459-46-1; 4-bromobenzyl bromide, 589-15-1; 3-fluorobenzyl bromide, 456-41-7; 4-(trifluoromethyl)benzyl bromide, 402-49-3; 3-cyanobenzyl bromide, 28188-41-2; 4-cyanobenzyl bromide, 17201-43-3; 1-propylnicotinamide bromide, 52047-79-7.

Nature of Substituent Effects in Nuclear Magnetic Resonance Spectroscopy. 2. Factor Analysis of Carbon-13 Chemical Shifts in Unsaturated and Aromatic Halides[1]

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The effect of halogen substitution on the ^{13}C chemical shifts of a variety of unsaturated and aromatic systems has been studied via factor analysis. Two principal factors and one smaller factor were found to correlate all of the data to within ±0.42 ppm. The halogen parameters obtained in the analysis agree well with those previously observed for saturated halides. The origin of the chemical shifts is discussed and it is shown that the second halogen substituent factor is linearly related to a variety of physical properties of halogen-containing compounds.

Substituent effects on the carbon-13 chemical shifts of unsaturated and aromatic systems have received a great deal of attention in the 20 years that have elapsed since the pioneering work of Lauterbur[3] and Spiesecke and Schneider.[4] The interest in such systems is due in large measure to the results of early studies which suggested that ^{13}C shielding might be linearly related to local electron density. Although the situation is certainly more complex than once thought, the effect of substituents on the ^{13}C chemical shifts of aromatic and unsaturated molecules continues to attract the interest of numerous investigators.

The vast body of ^{13}C shift data available for π-electron-containing systems has been extensively reviewed[5-11] and critical discussions are available on the analysis of substituent induced shifts in terms of simple additivity schemes,[5-9] calculated charge densities,[5-13] linear free-energy relationships of the Hammett–Taft type,[13,14] dual substituent parameter schemes,[14-16] electric field effects,[17] and many other empirical and semiempirical models.[5-11] Recent progress toward the development of a unifying theoretical mode for nuclear shielding[9,18-20] holds the

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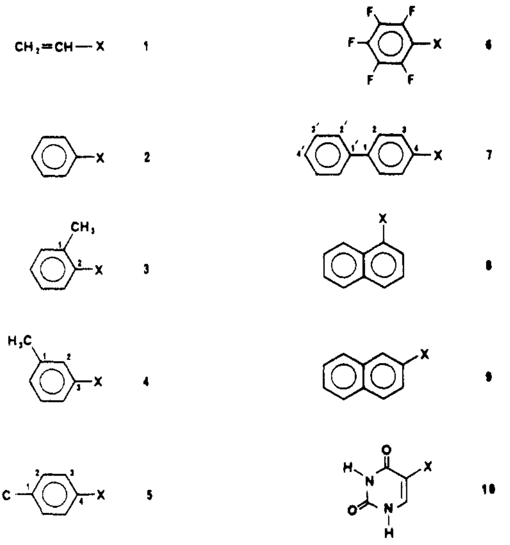

Figure 1. Structures of compounds used in this study.

promise of allowing for calculation of chemical shifts from first principles but, to date, the approaches can not adequately describe complex systems containing non-first-row elements.

In an attempt to bridge the gap between empirical models and theoretical treatments of nuclear shielding, we have been exploring substituent effects on ^{13}C chemical shifts using factor analysis.[21] This technique, which has been applied by a number of groups to probe solvent effects in NMR,[21-24] does not seem to have been previously used to analyze the effect of substituents on NMR chemical shifts. The results of an initial study of halogen substituent effects on ^{13}C shifts in aliphatic molecules[1] prompted us to extend the analysis to include unsaturated and aromatic halides. Herein we report that halogens affect ^{13}C chemical shifts in π-electron systems in three independent ways and these three intrinsic substituent factors are precisely those found responsible for the substituent effects in σ-electron systems.[1] In a subsequent article the nature of these halogen substituent effects and their relationship to other physical, chemical, and spectroscopic properties of halogen-containing molecules will be presented.[25]

Results

The molecules used in this study (Figure 1; X = H, F, Cl, Br, I) were selected to provide a representative set of unsaturated and aromatic halides. Although ^{13}C chemical shifts for all of these compounds are available in the literature,[3-11] much of the data was obtained under a variety of experimental conditions and they often suffer from an additional lack of accuracy due to referencing problems.[5-7] We have, therefore, redetermined the ^{13}C NMR spectra of the halobenzenes (**2**) and halotoluenes (**3**–**5**) as 2.0 M solutions in chloroform-*d* at 30 °C so as to hold constant the effects of solvent, concentration, and temperature. Chemical shift data for the remaining compounds used in this study were taken from the literature[26-30] and, with the exception of the shifts for the vinyl halides,[26] these data are considered to be accurate to within ±0.1–0.5 ppm.

Chemical shift data for the aromatic and vinylic halides (**1**–**10**; X = F, Cl, Br, I) are given in Table I and ^{13}C shifts for the parent molecules are listed in Table II. The effect generated upon replacement of a hydrogen in the parent molecule by the halogen is conveniently obtained by referring the chemical shift of each carbon in a given halide (δ_C^{RX}) to that of the analogous carbon in the parent (δ_C^{RH}). These differential chemical shifts, $\Delta\delta = \delta_C^{RX} - \delta_C^{RH}$, are presented in Table I and form the data set on which target-transformation factor analysis[21] was performed. Before proceeding with the results of the analysis, it is perhaps appropriate to present a brief overview of the method employed and its relationship to the more widely used technique of multiple regression analysis.

Factor analysis has as its objective the discovery of intrinsic linear relationships that exist within a body of data and the outcome of the analysis is a set of equations similar to those obtained via multiple regression. It must be noted, however, that factor analysis differs from regression analysis in two significant respects. First, a regression scheme, which proceeds by postulating the dependence of the data on some combination of parameters followed by analysis to determine the extent to which the initial postulate was valid, involves preselection of the independent variables. Factor analysis, in contrast, allows one to determine the nature of the independent variables (using target-testing[21]) after a correlation has been established. Secondly, the number of variables used in a multiple regression is arbitrarily chosen, whereas, in factor analysis, the actual number of factors needed to reproduce the experimental data (i.e., the intrinsic dimensionality of the problem[31]) is a direct consequence of the analysis step.

The procedure described in the previous article in this series[1] was followed in the analysis. The 232 $\Delta\delta$ values in Table I are expressed as 4 × 58 data matrix, $\mathbf{D}$, in which each row corresponds to a halogen and each column represents a carbon nucleus in molecules **1**–**10**. The objective of the first step of the analysis is to express each data point in $\mathbf{D}$ by a linear sum of products and this is accomplished by factorization of $\mathbf{D}$ into a $4 \times n$ row matrix, $\mathbf{H}$, and an $n \times 58$ column matrix, $\mathbf{M}$, such that $\mathbf{D} = \mathbf{HM}$. The $\mathbf{H}$ matrix, composed of four rows of n eigenvectors, may be associated with the halogen substituents and the $\mathbf{M}$ matrix, formed by 58 columns of n eigenvectors, corresponds to the molecular positions. Each of the eigenvectors (or factors[21]) has an associated eigenvalue, λ, indicating its relative importance. In this way the $\mathbf{H}$ and $\mathbf{M}$ matrices generated by factorization are composed of eigenvectors ranked according to their ability to account for the data.

The input data may of course be exactly reproduced by taking the product of $\mathbf{H}$ and $\mathbf{M}$ and this corresponds to a sum of products over all n factors:

$$\Delta\delta_{ik} = \sum_{j=1}^{n} h_{ij} m_{ik} \tag{1}$$

The data may also be reproduced, although with some small error, by deleting columns from $\mathbf{H}$ and rows from

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Table I. ^{13}C NMR Chemical Shifts of Aromatic and Unsaturated Halides

halide (no.)	position	chemical shifts[a]				differential chemical shifts[b]			
		F	Cl	Br	I	F	Cl	Br	I
vinyl[c] (1)	α	147.7	126.1	115.6	85.4	24.9	3.3	−7.2	−37.4
	β	88.5	117.4	122.1	130.5	−34.3	−5.4	−0.7	7.7
phenyl (2)	α	162.95	134.25	122.44	94.31	34.67	5.97	−5.84	−33.97
	β	115.33	128.55	131.42	137.21	−12.95	0.27	3.14	8.93
	γ	129.97	129.63	129.88	129.98	1.69	1.35	1.60	1.70
	δ	124.01	126.36	126.74	127.19	−4.27	−1.92	−1.54	−1.09
o-tolyl (3)	C(1) β	124.82	135.92	137.65	141.04	−12.91	−1.81	−0.08	3.31
	C(2) α	161.47	134.35	124.84	101.08	32.48	5.36	−4.15	−27.91
	C(3) β	114.95	129.01	132.22	138.70	−13.23	0.83	4.04	10.52
	C(4) γ	127.25	127.00	127.18	127.92	1.98	1.73	1.91	2.65
	C(5) δ	123.77	126.50	127.12	127.16	−4.41	−1.68	−1.06	−1.02
	C(6) γ	131.45	130.89	130.70	129.52	2.46	1.90	1.71	0.53
m-tolyl (4)	C(1) γ	140.40	139.74	139.98	139.96	2.67	2.01	2.25	2.23
	C(2) β	115.90	129.13	131.97	137.81	−13.09	0.14	2.98	8.82
	C(3) α	162.93	133.99	122.23	94.28	34.75	5.81	−5.95	−33.90
	C(4) β	112.23	125.53	128.39	134.26	−13.04	0.26	3.12	8.99
	C(5) γ	129.55	129.37	129.60	129.70	1.37	1.19	1.42	1.52
	C(6) δ	124.70	127.17	127.55	128.10	−4.29	−1.82	−1.44	−0.89
p-tolyl (5)	C(1) δ	133.32	136.16	136.57	137.01	−4.41	−1.57	−1.16	−0.72
	C(2,6) γ	130.30	130.32	130.69	130.97	1.31	1.33	1.70	1.98
	C(3,5) β	114.91	128.22	131.13	137.08	−13.27	0.04	2.95	8.90
	C(4) α	161.16	131.11	119.00	90.15	35.89	5.84	−6.27	−35.12
pentafluorophenyl[d] (6)	α	138.34	108.02	94.74	65.66	38.34	8.02	−5.26	−34.34
	β	138.34	144.81	145.61	147.88	−8.19	−1.72	−0.92	1.35
	γ	138.34	138.34	138.38	137.74	0.66	0.66	0.70	0.06
	δ	138.34	140.66	141.29	142.38	−3.55	−1.23	−0.60	0.49
4-halobiphenyl[e] (7)	C(1) δ	137.62	139.84	139.89	139.93	−3.63	−1.41	−1.36	−1.32
	C(2,6) γ	128.94	128.67	129.19	129.20	1.83	1.56	2.08	2.09
	C(3,5) β	115.66	129.16	132.09	138.14	−13.40	0.10	3.03	9.08
	C(4) α	162.94	133.20	121.36	92.84	35.33	5.69	−6.15	−34.67
	C(1′) ϵ	140.21	139.93	140.37	140.84	−1.04	−1.32	−0.88	−0.41
	C(2′,6′) ζ	127.03	127.02	126.99	126.91	−0.08	−0.09	−0.12	−0.20
	C(3′,5′) η	129.10	129.10	129.04	129.20	0.04	0.04	−0.02	0.14
	C(4′) θ	127.51	127.90	127.96	128.00	0.00	0.39	0.45	0.49
1-naphthyl[f] (8)	C(1) α	159.43	132.07	122.89	99.60	30.91	3.55	−5.63	−29.92
	C(2) β	110.18	126.94	130.70	138.19	−16.33	0.43	4.19	11.68
	C(3) γ	126.60	126.64	127.09	127.66	0.09	0.13	0.58	1.15
	C(4) δ	124.70	128.16	128.87	129.77	−3.82	−0.36	0.35	1.25
	C(5) δ	128.50	129.13	129.19	129.37	−0.02	0.61	0.67	0.85
	C(6) ϵ	127.79	127.57	127.54	127.48	1.28	1.06	1.03	0.97
	C(7) δ	127.23	127.98	128.22	128.49	0.72	1.47	1.71	1.98
	C(8) γ	120.79	124.64	127.32	132.36	−7.73	−3.88	−1.20	3.84
	C(9) β	124.33	131.36	132.56	134.90	−10.03	−3.00	−1.80	0.54
	C(10) γ	135.93	135.54	134.54	134.90	1.57	1.18	1.18	0.54
2-naphthyl[f] (9)	C(1) β	111.43	127.18	130.56	137.18	−17.09	−1.34	2.04	8.66
	C(2) α	161.38	131.87	120.14	91.80	34.87	5.36	−6.37	−34.71
	C(3) β	116.73	127.18	129.76	134.90	−9.78	0.67	3.25	8.39
	C(4) γ	131.39	130.51	130.65	130.31	2.87	1.99	2.13	1.79
	C(5) ϵ	128.68	128.51	128.63	128.49	0.16	−0.01	0.11	−0.03
	C(6) ζ	126.02	127.00	127.23	127.24	−0.49	0.49	0.72	0.73
	C(7) ϵ	127.77	127.78	127.80	127.44	1.26	1.27	1.29	0.93
	C(8) δ	128.05	127.78	127.80	127.44	−0.47	−0.74	−0.72	−1.08
	C(9) γ	135.13	134.90	135.42	135.73	0.77	0.54	1.06	1.37
	C(10) δ	131.49	132.56	132.79	132.80	−2.87	−1.80	−1.57	−1.56
5-halouracil[g] (10)	C(2) δ	151.04	151.56	151.76	152.24	−1.90	−1.38	−1.18	−0.70
	C(4) β	158.87	160.89	161.03	162.48	−6.53	−4.51	−4.37	−2.92
	C(5) α	140.79	106.84	95.30	68.46	39.69	5.74	−5.80	−32.64
	C(6) β	127.27	140.65	143.11	149.97	−15.91	−2.53	−0.07	4.79

[a] In parts per million from internal Me_4Si. [b] $\Delta\delta = \delta_C^{RX} - \delta_C^{RX}$, negative values indicate upfield shifts from the parent hydrocarbon. [c] Reference 26. [d] Reference 27. [e] Reference 28; data converted to Me_4Si scale, using $\delta_C^{C_6H_6} = 128.5$ ppm (ref 6). [f] Reference 29. [g] Reference 30; data converted to Me_4Si scale, using $\delta_C^{CS_2} = 193.7$ ppm (ref 6).

M (*i.e., by truncation of the sum given in eq 1*). The eigenvalue associated with each of the *n* factors provides a guide to the number of factors which may be eliminated without leading to unacceptably large errors. Thus, the number of eigenvectors which are retained (i.e., the number of terms remaining in eq 1) corresponds to the number of independent[1,21] factors needed to reproduce the experimental data within a given limit of error.

Analysis of the $\Delta\delta$ values in Table I revealed that two major substituent factors having eigenvalues of 33 and 23, respectively, account for 96.9% of the total variance in the data set and reproduce the original differential shifts with a root-mean-square (rms) error of ±1.28 ppm. Inclusion of a third, less significant ($\lambda = 1.3$) factor in the correlation reduces the rms error to ±0.42 ppm and reproduces 99.2% of the variance. From these results, summarized in Table III, it may be concluded that only three independent substituent factors are needed to fit the shift data to within the experimental error. Thus, a correlation equation employing the eigenvectors could be written using only the first three terms of the sum given in eq 1. Transformation of these abstract terms into recognizable parameters con-

Table II. ^{13}C NMR Chemical Shifts of Parent Molecules

molecule	position	^{13}C chemical shift[a]
ethylene[b] (**1**)		122.8
benzene (**2**)		128.28
toluene (**3**, **4**, **5**)	ipso	137.73
	ortho	128.99
	meta	128.18
	para	125.27
	CH_3	21.40
pentafluorobenzene[c] (**6**)	ipso	100.00
	ortho	146.53
	meta	137.68
	para	141.89
biphenyl[d] (**7**)	ipso	141.25
	ortho	127.11
	meta	129.06
	para	127.51
naphthalene[e] (**8**, **9**)	C(1,4,5,8)	128.52
	C(2,3,6,7)	126.51
	C(9,10)	134.36
uracil[f] (**10**)	C(2)	152.94
	C(4)	165.40
	C(5)	101.10
	C(6)	143.18

[a] In parts per million from internal Me_4Si. [b] Reference 26. [c] Reference 27. [d] Reference 28. [e] Reference 29. [f] Reference 30.

Table III. Statistical Analysis of Factorization

no. of factors	eigenvalue,[a] λ	cumulative % variance[b]	rms error in reproduced data
1	33.03	56.9	
2	23.14	96.9	1.28
3	1.34	99.2	0.42
4	0.48	100.0	0.00
5	5.2×10^{-5}		

[a] The remaining factors have vanishingly small eigenvalues. [b] Percentage of total variance in the ^{13}C shifts (58 nuclei) accounted for by the data reduction. The variance accounted for by each factor is given by $\lambda_i / \Sigma_{i=1}^{n} \lambda_i$, where λ_i is the eigenvalue of factor i and n is the number of factors needed to exactly reproduce the data. The cumulative percent variance is analogous to r^2 (×100) for a regression equation.

stitutes the second stage of the analysis and for this purpose we have used the technique of target-testing described in detail by Malinowski and Howery.[21]

Target-testing involves choosing test vectors to represent the principal substituent factors identified in the initial factorization. The extent to which the test vectors adequately describe the abstract factors is adjudged by the ability to transform the eigenvectors of the **H** matrix into the test vectors by rotation in factor space. When the target is correctly chosen, the best-fit rotation[21] of the row vectors of **H** will give a set of factors which closely match the values of the test vectors. The vectors chosen for target analysis of the **H** matrix were those found to be responsible for halogen substituent effects on ^{13}C shifts in aliphatic systems.[1] Thus, a constant (1, 1, 1, 1) was taken as a test vector for the most important halogen factor and an arithmetic progression (1, 2, 3, 4) was used as a test for the second significant factor. The third substituent factor, which is not as well defined as the other two by virtue of its small eigenvalue, was approximated as (1, 0, 0, 1) by analogy with the aliphatic halide analysis.[1] Target transformation of these test vectors gave the results listed in Table IV. The three halogen parameters (a_1, a_2, a_3) are intrinsic to the substituents and characterize the three independent ways in which halogen affects ^{13}C shifts in π systems. A corresponding rotation of the reduced (3 × 58) **M** matrix gave a set of cofactors or attenuation parameters (b_1, b_2, b_3) listed in Table V. These molecular cofactors may be used to probe the structural dependence of the substituent effects since they reflect the sensitivity of each carbon nucleus in molecules **1**–**10** to the effect of each halogen factor. It should be noted that the a_1, a_2, and a_3 factors identified in this target transformation are virtually identical with the halogen parameters obtained from analysis of the substituent effects in aliphatic halides.[1]

Table IV. Halogen Substituent Parameters (Factors) Resulting from Target Tests of the Three-Factor Solution

halogen	test vectors			halogen substituent parameters[a]		
				a_1	a_2	a_3
F	1.0	1.0	1.0	1.008	0.970	0.944
Cl	1.0	2.0	0.0	0.949	2.201	0.038
Br	1.0	3.0	0.0	1.043	2.830	−0.032
I	1.0	4.0	1.0	0.996	4.017	1.003

[a] Used in conjunction with the molecular attenuation cofactors (Table V), these parameters reproduce the experimental $\Delta\delta$ shifts with a rms error of 0.42 ppm.

The overall result of the factor analysis is the linear correlation given by eq 2. The differential chemical shifts

$$\Delta\delta_{xk} = a_{x1}b_{1k} + a_{x2}b_{2k} + a_{x3}b_{3k} \qquad (2)$$

are reproduced by a three-term sum of products involving the three halogen factors (a_{xj}) listed in Table IV and the three molecular altenuation cofactors for each nucleus (b_{jk}) given in Table V. Also included in Table V are the individual rms errors of the differential chemical shifts calculated via eq 2 for each type of ^{13}C nucleus in molecules **1**–**10**. Overall, the experimental data are reproduced by the three-factor correlation to within ±0.42 ppm and most of this error is due to deviations between calculated and experimental $\Delta\delta$ values at the α position (±1.09 ppm). A comparison between the observed $\Delta\delta$'s at the α, β, γ, etc. positions and those calculated by using eq 2 is detailed in Table VI.

Obviously, the $\Delta\delta$ values could be approximated by employing only the first two terms of eq 2. The simplification realized by this further reduction increases the overall rms error of the correlation to ±1.28 ppm. However, since the largest deviations are found at those positions having the widest range of substituent induced shifts (77 and 46 ppm for the α and β nuclei, respectively), such an error may be tolerated under most circumstances. Moreover, since the first halogen factor, a_1, is essentially a constant for all halogens, the two-term correlation reduces the analysis to a plot of $\Delta\delta$ against the a_2 factors, leading to a slope (b_2 values) and an intercept (b_1 values).

An additional dividend of the factor analysis are the molecular cofactors (b's) which, as noted above, may be used to investigate the structural dependence of each halogen factor. Examination of b values in Table V reveals that there is a remarkable consistency in both sign and magnitude of these sensitivity parameters for nuclei at a given number of bonds from the halogen. In fact, with but the few exceptions discussed below, the α, β, γ, and δ carbons can be distinguished simply by reference to their b values. Such a regularity in cofactor values represents a "cluster" in the jargon of target-factor analysis[21] and indicates that the structural elements are related. On the basis of this clustering (Table VII) it might be expected that a regression analysis in terms of the position of a ^{13}C nucleus relative to the substituent would be successful and, indeed, such parameterizations have been realized.[5-7,9]

Table V. Molecular Attenuation Cofactors from Three-Factor Analysis

molecule (no.)			molecular attenuation factors			
			b_1	b_2	b_3	rms error
vinyl (1)		α	49.33	−20.35	−4.89	1.10
		β	−37.48	13.62	−9.72	0.43
phenyl (2)		α	56.58	−22.43	−0.35	1.25
		β	−16.26	7.11	−3.46	0.08
		γ	1.45	0.01	0.21	0.05
		δ	−4.34	1.03	−0.91	0.03
o-tolyl (3)	C(1)	β	−14.24	5.26	−3.64	0.20
	C(2)	α	50.28	−19.70	1.07	0.73
	C(3)	β	−17.07	7.73	−3.52	0.12
	C(4)	γ	1.03	0.31	0.36	0.04
	C(5)	δ	−4.16	1.11	−1.32	0.09
	C(6)	γ	3.38	−0.62	−0.34	0.06
m-tolyl (4)	C(1)	γ	2.47	−0.13	0.30	0.05
	C(2)	β	−16.42	7.12	−3.44	0.14
	C(3)	α	56.45	−22.43	−0.14	1.22
	C(4)	β	−16.39	7.16	−3.46	0.14
	C(5)	γ	1.17	0.06	0.13	0.04
	C(6)	δ	−4.42	1.10	−0.92	0.01
p-tolyl (5)	C(1)	δ	−4.39	1.20	−1.15	0.01
	C(2)	γ	0.95	0.23	0.12	0.06
	C(3)	β	−16.70	7.21	−3.42	0.12
	C(4)	α	58.25	−23.20	−0.06	1.23
pentafluorophenyl (6)		α	61.27	−23.78	0.00	1.68
		β	−9.12	3.08	−1.96	0.17
		γ	1.16	−0.19	−0.33	0.01
		δ	−4.24	1.32	−0.57	0.06
4-halobiphenyl (7)	C(1)	δ	−3.27	0.74	−1.05	0.07
	C(2,6)	γ	1.58	0.10	0.11	0.10
	C(3,5)	β	−16.89	7.31	−3.46	0.13
	C(4)	α	57.40	−22.87	−0.10	1.17
	C(1′)	ϵ	−1.64	0.22	0.36	0.20
	C(2′,6′)	ζ	−0.01	−0.04	−0.04	0.01
	C(3′,5′)	η	−0.07	0.03	0.08	0.03
	C(4′)	θ	0.02	0.16	−0.17	0.02
1-naphthyl (8)	C(1)	α	48.97	−19.83	0.90	0.51
	C(2)	β	−20.69	9.11	−4.32	0.14
	C(3)	γ	−0.53	0.36	0.26	0.12
	C(4)	δ	−4.17	1.65	−1.22	0.01
	C(5)	δ	−0.07	0.28	−0.21	0.05
	C(6)	ϵ	1.30	−0.10	−0.01	0.03
	C(7)	δ	0.55	0.41	−0.23	0.04
	C(8)	γ	−12.11	3.81	0.66	0.60
	C(9)	β	−11.07	3.43	−2.21	0.03
	C(10)	γ	2.02	−0.33	−0.14	0.10
2-naphthyl (9)	C(1)	β	−20.79	8.37	−4.27	0.10
	C(2)	α	56.77	−22.72	−0.01	1.14
	C(3)	β	−12.97	5.91	−2.46	0.04
	C(4)	γ	2.93	−0.34	0.24	0.04
	C(5)	ϵ	0.20	−0.06	0.00	0.06
	C(6)	ζ	−0.40	0.40	−0.47	0.01
	C(7)	ϵ	1.55	−0.10	−0.19	0.03
	C(8)	δ	−0.23	−0.19	−0.06	0.07
	C(9)	γ	0.28	0.21	0.25	0.16
	C(10)	δ	−2.76	0.43	−0.52	0.08
5-halouracil (10)	C(2)	δ	−2.27	0.39	−0.01	0.07
	C(4)	β	−7.38	1.16	−0.22	0.03
	C(5)	α	59.47	−23.60	2.84	0.86
	C(6)	β	−18.28	6.72	−4.01	0.14

Table VI. Comparison of Experimental ^{13}C Shifts and Those Calculated by Using the Three-Factor Halogen Parameters

data set	no. of carbon nuclei in set[a]	range of $\Delta\delta$, ppm	rms error of recalcd $\Delta\delta$,[b] ppm
all positions	58	77.1	0.42
α	10	77.1	1.09
β	15	46.0	0.13
γ	13	11.6	0.11
δ	12	6.4	0.05
ϵ and higher	8	2.6	0.05

[a] The actual number of ^{13}C shifts for each set is 4 times this value. [b] $\Delta\delta = a_1b_1 + a_2b_2 + a_3b_3$. The halogen substituent parameters (a's) are given in Table IV and the molecular attenuation cofactors (b's) are given in Table V.

Table VII. Range of Molecular Attenuation Cofactors at Various Positions

position of nucleus	b_1	b_2	b_3
α	55 ± 6	−22 ± 2	−2 ± 3
β	−22 ± 15	7 ± 6	−5 ± 5
γ^a	1.8 ± 1.6	−0.2 ± 0.5	0 ± 0.3
δ^b	−2.2 ± 2	0.8 ± 0.9	−0.7 ± 0.6

[a] Two exceptions to these ranges are found for C(3) and, particularly, C(8) of the 1-naphthyl system (8). [b] An exception to these ranges is found at C(7) of the 1-naphthyl molecule.

Discussion

The similarity in values of substituent parameters obtained in this study and in the analysis of aliphatic halides[1] implies that the same (or linearly related) effects are responsible for shielding changes in both σ and π systems. Consequently it would be expected that the a_2 factors, which control changes in ^{13}C shift as the halogen is varied from F to I, should be linearly related to empirical increments for the halogens derived from regression analysis, and this is in fact the case. For example, plots of the a_2 parameters (Table IV) vs. the halogen increments found by Ejchart[32] or the "Δx values" obtained by Litchman and Grant[33] give linear relationships with correlation coefficients (r) of 0.998 and 0.993, respectively. This observation serves to place the present study in perspective since it demonstrates that the information available from regression analysis is contained in just one of the parameters found by factorization.

The halogen factors identified above are a measure of the independent effects responsible for the differential shifts. The analysis does not of course establish the physical basis for these substituent effects. Interpretation of the results involves determination of the nature of the halogen properties reflected in the factors and this, in turn, requires a knowledge of the ways in which a substituent may affect ^{13}C shielding.

In principle, the physical significance of the halogen factors should follow directly from a comparison of the analysis data with the predictions of theory. A valid model for the effect of substituents on ^{13}C shielding will include terms whose values for halogen as the substituent must be linearly related to the factors obtained in the analysis.

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(32) Ejchart, A. *Org. Magn. Reson.* **1980**, *13*, 368.

(33) Litchman, W. M.; Grant, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1400.

In this connection it should be noted that since the factorization involved no assumptions concerning the origin of the ^{13}C shifts, the results are not a priori supportive of any particular model for nuclear screening. Thus, comparison of the halogen factors listed in Table IV with values for the substituent-dependent terms of theory serves a dual purpose; the analysis results may be used to evaluate the models for ^{13}C shielding and, conversely, valid theory provides an insight into the nature of the effects reflected in the factors. Attention will focus on the a_2 factors since, inter alia, they are most characteristic of shielding changes affected by variation in the halogen. The a_3 parameters contribute little ($\lambda = 1.34$) to the correlation and are not well defined in the analysis. For this reason, the a_3 factors will not be treated beyond noting that they have been previously discussed in connection with the results of the factor analysis of aliphatic systems.[1]

Most treatments of ^{13}C shielding partition the screening constant into diamagnetic (σ^d) and paramagnetic (σ^p) components.[5-9,18-20] Variation in σ^p is generally acknowledged to be the dominant contributor to changes in ^{13}C shift.[5-9,18-20] This term is given by the Karplus–Pople formalism[34] as

$$\sigma^p = -\tfrac{1}{2}(e\hbar/mc)^2\langle r^{-3}\rangle_{2p}Q/\Delta E$$

where $\langle r^{-3}\rangle$ is the expectation value for the inverse cube of the 2p-orbital radius, Q represents bond-order elements, and ΔE is the mean electronic excitation energy for relevant transitions.

The $\langle r^{-3}\rangle$ term provides the rationale, albeit implicit in most studies, for attempted correlations of ^{13}C shifts with charge density[5-13] and Hammett–Taft substituent parameters.[13-16] While it is clear from the expression for σ^p that these correlations are possible only to the extent ΔE and the bond-order terms remain constant (or vary in a mutually compensating way), many such relationships have been developed for substituted aromatics.[4-16] The factor analysis results strongly suggest that empirical correlations of this sort should abound for halogen containing molecules. The a_2 factors are in fact linearly related to the inductive (σ_I, $r = 0.997$),[35] resonance ($\sigma_R{}^0$, $r = 0.959$),[36] and steric (E_s, $r = 0.983$)[37] substituent constants for the halogens! In view of this unexpected linearity among terms, it is not clear what insight, if any, is provided by correlations of substituent parameters with ^{13}C shift in unsaturated halides.

Determination of a value for ΔE is a critical if somewhat arbitrary aspect of ^{13}C shielding calculations. The σ^p component is a strong function of this variable; a decrease of only 1 eV in ΔE results in a paramagnetic shift (on the order of 20–30 ppm),[7,9,18,19,38] which is comparable to that produced by a 0.25-e change in charge density. Despite the fact that small variations in ΔE can easily mask other contributions to shielding, the term is typically taken to be a constant for related structures.[5,7-9,18,19,34] While it is clear that substituents can dramatically affect the magnitude of ΔE (hence σ^p) by introducing low energy transitions not originally present in the parent molecule,[19,38-40] it is difficult to establish the relationship between ΔE and substituent induced variation in the energies of these transitions.[38-40] The mean excitation energy is, after all, a computational artifact[34] and the magnetic-dipole allowed excitations which contribute to this term[34] are weak (or absent) in electronic spectra. Be that as it may, the presence of nonbonded electrons on halogen substituents should tend to decrease the magnitude of ΔE and increase σ_p. The lowest energy magnetically active excitations in aromatic halides involve the nonbonded halogen orbital that is in the plane of the ring (i.e., $n_{\parallel} \rightarrow \pi^*$). The effect of substituents on the energy of this excitation may be estimated[38-40] from the ionization potentials (IP's) of the $n_{\parallel}$ orbital in the halobenzenes. The IP's for $n_{\parallel}$ of **2** (X = F, Cl, Br, I) are known[41] and the reciprocals of these values are linearly related ($r = 0.985$) to the a_2 halogen factor identified in this analysis. It might, therefore, be reasonably concluded that the a_2 factors reflect changes in ΔE (or, more precisely, in the excitation energies which it approximates[34]) as the substituent is varied from F through I. It is of some interest to further note that the a_2 parameters are also related in the linear way to both the reciprocals of the IP's for the $n_{\perp}$ orbitals of the halobenzenes[41] ($r = 0.984$) and, as would be expected from the substituent–constant correlations noted above, the reciprocals of the lowest IP's for the π orbitals in these molecules[41] ($r = 0.947$).

Correlation of the a_2 factors with calculated charge densities at various molecular positions in unsaturated halides was not attempted. It is expected, however, that such relationships would also be linear since it has been long known tht plots of calculated π- or total-charge densities vs. Hammett substituent constants show reasonably linear trends.[3-16] The localized charges at C(α) in unsaturated halides, obtained simply from the C–X bond dipoles[42] and C–X bond lengths,[43] are related in a remarkably linear way[44] ($r = 0.998$) to the a_2 factors. This correlation is of some significance since electric field effects are typically evaluated from bond dipoles with appropriate charges localized on each atom.[17,45] Thus, the a_2 parameters must be related linearly to the calculated effect of substituent induced electric fields.

Faced with this plethora of linear correlations, attempts were made to find substituent-dependent terms of shielding theory which are not linear when plotted against the a_2's. Mason has suggested[46] that adjacent atoms may

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(34) (a) Karplus, M.; Pople, J. A. *J. Chem. Phys.* **1963**, *38*, 2803. (b) Pople, J. A. *Mol. Phys.* **1964**, *7*, 301.

(35) The inductive substituent constants (σ_I) for the halogens (F, Cl, Br, I) are as follows: 0.52, 0.47, 0.45, and 0.39, respectively [Fujita, T.; Nichioka, T. *Prog. Phys. Org. Chem.* **1976**, *12*, 49]. A plot of σ_I vs. the a_2 factors in Table IV is linear with $r = 0.997$.

(36) The resonance substituent constants ($\sigma_R{}^0$) for the halogens (F, Cl, Br, I) are −0.34, −0.23, −0.19, and −0.16, respectively [Exner, O. In "Correlation Analysis in Chemistry"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York; p 439]. A plot of $\sigma_R{}^0$ vs. the a_2 factors is linear with $r = 0.959$. The poorer correlation found for this relationship may well reflect the fact that $\sigma_R{}^0$ is the least certain of all σ constants.

(37) The steric substituent constants (E_s) for the halogens (F, Cl, Br, I) are −0.46, −0.97, −1.16, and −1.40, respectively [Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, 91]. E_s is linearly related to the a_2 factors with $r = 0.983$.

(38) Baird, N. C.; Teo, K. C. *J. Magn. Reson.* **1976**, *24*, 87.

(39) Bloor, J. E.; Breen, D. L. *J. Phys. Chem.* **1968**, *72*, 716.

(40) Mason, J. *J. Chem. Soc., Faraday. Trans. 2* **1979**, 607.

(41) The IP's of the $\eta_{\parallel}$ orbital electrons in the halobenzenes (**2, X** = F, Cl, Br, I) are 14.1, 11.42, 10.65, and 9.78 eV, respectively. The corresponding IP's of the $n_{\perp}$ orbital electrons are 14.1, 11.76, 11.20, and 10.36 eV, respectively. The lowest energy π-orbital IP's for thse molecules are 9.50, 9.31, 9.25, and 8.78 eV, respectively [Baker, A. D.; May, D. P.; Turner, D. W. *J. Chem. Soc. B* **1968**, 22].

(42) The C–X bond moments (X = F, Cl, Br, I) are 1.41, 1.46, 1.38, and 1.19 D, respectively [Smyth, C. P. "Dielectric Behavior and Structure"; McGraw-Hill: New York, 1955].

(43) The average aromatic C–X bond lengths (X = F, Cl, Br, I) are 1.33, 1.70, 1.85, and 2.05 Å, respectively. Cf. Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley-Interscience: New York, 1972; p 107.

(44) The point charges at C(α) in unsaturated halides (X = F, Cl, Br, I) are 0.221, 0.179, 0.155, and 0.121 e, respectively. These values are obtained from $\mu/r{\cdot}e$, where μ is the bond moment (ref 42), r is the average C–X bond length (ref 43), and e is the electron charge.

(45) (a) Schneider, H.-J.; Freitag, W. *J. Am. Chem. Soc.* **1977**, *99*, 8363. (b) Gschwendtner, W.; Schneider, H.-J. *J. Org. Chem.* **1980**, *45*, 3507.

cause significant variation in σ^d particularly when they are of high atomic number, Z, and this approach has been successful in rationalizing the anomalous shifts engendered by fourth- and fifth-row atoms ("heavy-atom effect").[7-9,46] The correction to be applied to the free-atom Lamb term is given by the semiempirical relationship of Flygare and Goodisman:[47]

$$\sigma^d = \sigma^d(\text{free atom}) + (e_2/3mc_2)\sum Z_k/r_k$$

where the constants have their usual meaning and the Z/r term represents the atomic number of the directly attached atom divided by the length of its bond to the carbon. The values of this correction term for the halogens[48] are linearly related to the a_2 factors ($r = 0.964$).

It may be concluded that the a_2 parameters identified by factor analysis are linearly related to all significant substituent-dependent terms of theory! Unfortunately, experimental shielding tensors are not available for any of the ^{13}C nuclei in the halobenzenes (**2**) or vinyl halides (**1**) but, as noted in a previous article,[1] the a_2 factors are linearly related to the experimental ^{13}C tensors of the methyl halides.[49] The b_2 molecular cofactors, which reflect the sensitivity of each molecular position to the effect characterized by a_2, are consistent with virtually all of the possible interpretations of the a_2 factors since they alternate in sign and monotonically decrease in magnitude with increasing distance from the substituent. Any definitive conclusion as to the nature of the effect reflected in a_2 must, therefore, await the results of further factor analytical studies using nonhalogen substituents. These investigations are in progress.

In view of the difficulties associated with physical interpretation of the variable a_2 parameters, any discussion of the effectively constant a_1 factors beyond that given previously[1] would not be productive. We have suggested that these terms may reflect the essentially constant polar effect of halogens,[1] but this supposition must also await confirmation from the results of studies on substituent induced ^{13}C shifts in non-halogen-containing molecules.

The linear interrelationships among the a_2 factors, substituent constants, reciprocals of ionization potentials, charge densities, and contributions of σ^d might be accidental, but this seems highly unlikely. In any event, these linear correlations are not confined to quantities which affect ^{13}C shielding. Virtually all physical and spectroscopic properties of halogen-containing molecules are linearly related to each other and to the a_2 parameters! The consequences of such linear relationships are explored in a following paper.[25]

Experimental Section

Carbon-13 magnetic resonance spectra were recorded on a Bruker WH-90 spectrometer in the FT mode operating at 22.6 MHz by using 2.0 M solutions of compounds **2**-**5** (X = F, Cl, Br, I) in $CDCl_3$ at 30 °C and are referenced to internal Me_4Si. Assignments are based on the known chemical-shift substituent effects in these systems.[5-11]

The halides used in this study were either available from commercial sources and purified prior to use or were prepared from the appropriate aniline, via its diazonium salt, by classical methods.

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Registry No. 2 (X = F), 462-06-6; **2** (X = Cl), 108-90-7; **2** (X = Br), 108-86-1; **2** (X = I), 591-50-4; **3** (X = F), 95-52-3; **3** (X = Cl), 95-49-8; **3** (X = Br), 95-46-5; **3** (X = I), 615-37-2; **4** (X = F), 352-70-5; **4** (X = Cl), 108-41-8; **4** (X = Br), 591-17-3; **4** (X = I), 625-95-6; **5** (X = F), 352-32-9; **5** (X = Cl), 106-43-4; **5** (X = Br), 106-38-7; **5** (X = I), 624-31-7.

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(46) (a) Mason, J. *J. Chem. Soc. A* **1971**, 1038. (b) Mason, J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1671. (c) Mason, J. *Org. Magn. Reson.* **1977**, *10*, 188. (d) Mason, J. *Adv. Inorg. Chem. Radiochem.* **1979**, *22*, 199.

(47) Flygare, W. H.; Goodisman, J., *J. Chem. Phys.* **1968**, *49*, 3122.

(48) The value of Z/r for the halogen substituents (X = F, Cl, Br, I) follows directly from the atomic numbers and bond lengths (ref 43): 6.77, 10.00, 18.92, and 25.85 amu·Å^{-1}, respectively.

(49) Appleman, B. R.; Dailey, B. P. *Adv. Magn. Reson.* **1974**, *7*, 310.

Intrinsic Linear Interrelationships among Physical and Spectroscopic Properties of Halogen-Containing Molecules[1]

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The effect of halogen substituents on the value of liquid and/or vapor phase properties, both physical and spectroscopic, of halogen-containing molecules has been studied by factor analysis. Two principal factors, a_1 and a_2, were found to account for 99.9% of the total variance in the data. The halogen parameters obtained in the analysis are essentially a constant for all halogens ($a_1 = 1.000 \pm 0.015$) and an arithmetic progression of integers ($a_2 \approx 1.0, 2.0, 3.0$, and 4.0 for X = F, Cl, Br and I, respectively). These factors agree well with those previously obtained from factor analysis of ^{13}C chemical shifts of organic halides. The analysis reveals that there is an intrinsic linear interrelationship among virtually all measurable liquid and/or vapor phase properties of halogen-containing molecules. A qualitative rationale for this finding is offered in terms of the dominant role of polarizability in determining changes in the magnitude of property values as the halogen substituent is varied.

Factor analysis of ^{13}C chemical shifts for a variety of aliphatic, unsaturated, and aromatic halides[1,3] has revealed that the substituent induced shifts are controlled by two principal halogen factors. The most important parameter