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

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The ^{13}C spectra of 18 sets of aliphatic and alicyclic halides (F, Cl, Br, I) have been obtained as 2 M solutions in $CDCl_3$ and have been assigned. The differences in chemical shift with respect to the parent hydrocarbons ($\Delta\delta$) have been analyzed by the use of factor analysis. This technique leads to two sets of parameters: "intrinsic" substituent effects (a values) characteristic of the halogens and attenuation parameters (b values) which reflect the sensitivity of each molecular position to the substituent effects. In the present case it was found that only three-substituent-effect terms for each halogen are needed to correlate all of the data. The chemical shifts are related to the parameters by $\Delta\delta_{xi} = a_{x1}b_{1i} + a_{x2}b_{2i} + a_{x3}b_{3i}$ where x refers to the halogens and i refers to the molecular positions. The first substituent parameter (a_1) is essentially a constant for all of the halogens and appears to be related to the polar effect of halogen vis-à-vis hydrogens. The corresponding attenuation parameters (b_1) represent the sensitivity of each molecular position to polar effects of the halogens. The second substituent parameter (a_2) increases approximately linearly on going from fluorine to iodine, controls the differences in $\Delta\delta$ for the series of halides, and appears to be related to the "freeness" of the valence electrons about the halogens. The third parameter (a_3) is considerably less significant than the others. An analysis of the effect of the structural changes on the molecular attenuation parameters (b_1–b_3) reveals that the two most important substituent parameters are each transmitted to the α, β, and γ positions via the same or linearly related mechanisms. The a_2 halogen factors are linearly related to a variety of non-NMR parameters characteristic of the halogens (reciprocals of the ionization potentials of CH_3X, wavelength of the first electronic transition of CH_3X, C–X bond polarizabilities, and atomic contributions to molar diamagnetic susceptibilities) as well as the diamagnetic and paramagnetic susceptibilities derived from NMR measurements.

Over a quarter of a century has passed since the first observations of the chemical shift were reported.[4] Relying for the most part on empirically derived correlations, chemists have exploited this phenomena as a powerful and sensitive probe of molecular structure.[5-10] In particular, the rapid development of carbon-13 magnetic resonance has resulted in the formation of numberous structure–shift relationships,[7-12] which generally are based on linear-regression analysis of shift data following the approach pioneered by Grant and co-workers.[13-17] The correlations are expressed as a set of additive parameters which allow for the calculation of ^{13}C chemical shifts in terms of both the molecular geometry and the nature of substituents at the α, β, γ, etc. positions. These simple additivity relationships, while of undeniable importance and utility, do not in themselves provide an explanation of nuclear shielding. Clearly, the successful prediction of a chemical shift neither requires nor implies an understanding of the origin of the chemical shift. Despite extensive theoretical investigations at both the ab initio and semiempirical levels,[18-22] the origin of the chemical shift in complex molecules remains obscure.

In view of the difficulties with theoretical interpretation, many investigators have attempted to experimentally elucidate the factors responsible for ^{13}C shifts by systematic study of substituent effects.[11,12,21] Such work has furnished the structure–shift correlations which provide a foundation for routine application of ^{13}C NMR,[7-17] but, unfortunately, there are almost as many explanations of the observed correlations as there are investigators in the area! Thus, various mechanisms have been proposed to account for ^{13}C shieldings in terms of models involving steric and/or geometric factors,[19,23-25] electrical field effects,[11,12,26-30]

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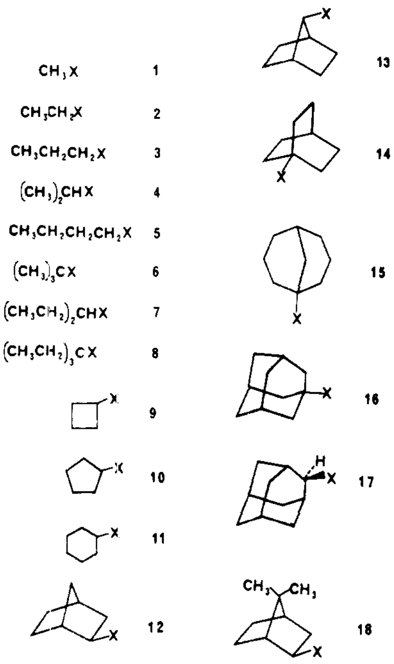

Figure 1. Structures of compounds used in this study.

charge distribution,[11,12,31-33] separation of diamagnetic and paramagnetic contributions,[34] anisotropy of neighboring groups and bonds,[11,21,35] heavy-atom effects,[11,15,36] and other factors.[11,12,21]

In order to obtain a relatively simple subset of data which might be amenable to a detailed analysis, we have investigated the ^{13}C NMR spectra of monosubstituted alkyl halides.[1,37] The cylindrical symmetry of the C–X bond simplifies conformational analysis. Moreover, since the C–X bond dipoles are of similar magnitude,[38] the electrical field effect[26-30] produced by the halogens should be of similar magnitudes past the α-position.

Results

Figure 1 contains the structures of the molecules used in this study. With the exception of the fluoride of **18**, the ^{13}C chemical shifts of a complete series (X = H, F, Cl, Br, I) were determined for each structure (**1**–**18**). Although data for the parent alkanes and a number of the halides are available in the literature, they were determined under a variety of experimental conditions which are known to affect chemical shifts.[11,39-41] Therefore, we have redetermined the ^{13}C shifts of most of the simple alkyl halides and have obtained the ^{13}C resonances for a number of additional halides. All spectra were recorded as 2.0 M solutions in chloroform-*d* at 30 °C so as to minimize solvent, concentration, and temperature effects on the differences in chemical shift. In those cases where data reported by other investigators were determined under similar conditions, the ^{13}C shifts[42-44] have been incorporated into the present study to provide a fairly comprehensive set of data.

The chemical shift data for the alkyl halides (**1**–**18**; X = F, Cl, Br, I) are presented in Table I, and data for the parent hydrocarbons are given in Table II. It is convenient to refer the chemical shift of each carbon in a given halide (δ_C^{RX}) to that of the analogous carbon in the parent hydrocarbon (δ_C^{RH}). The resulting differential chemical shifts, $\Delta\delta = \delta_C^{RX} - \delta_C^{RH}$, are also given in Table I. These $\Delta\delta$ values give the effect of replacement of a hydrogen atom in a given structure by halogen, and such values have been termed "substituent effects".[7-12]

An analysis of a set of data such as that given in Table I usually proceeds via postulating a dependence on some measurable quantities followed by a regression analysis to determine to what extent the postulate was valid. A fundamental difficulty with this approach is that one does not know how many independent variables are required in order to fit the data. An alternate approach, factor analysis,[45] circumvents this difficulty and is readily applied to sets of data of the type presented in Table I.

In factor analysis, one begins with an $m \times n$ data matrix **D** (in the present case n is the number of molecular positions for which chemical shifts are available and m = 4, the number of substituents used). The matrix **D**, is multiplied by its transpose, $\mathbf{D}^\dagger$, to give a square ($n \times n$) correlation matrix, **C**. Diagonalization of **C** gives an eigenvector matrix **B** and the eigenvalue array λ.

$$\mathbf{D}^\dagger\mathbf{D} = \mathbf{C} \qquad (1)$$

$$\mathbf{B}^{-1}\mathbf{C}\mathbf{B} = \lambda \qquad (2)$$

Substituting (1) into (2) gives

$$\mathbf{B}^{-1}\mathbf{D}^\dagger\mathbf{D}\mathbf{B} = \lambda$$

Since the eigenvectors are orthogonal, this may also be written as

$$\mathbf{B}^\dagger\mathbf{D}^\dagger\mathbf{D}\mathbf{B} = \mathbf{H}^\dagger\mathbf{H} = \lambda$$

where **DB** = **H**. Now, the original data matrix may be written as

$$\mathbf{D} = \mathbf{H}\mathbf{B}^{-1}$$

or

$$\mathbf{D} = \mathbf{H}\mathbf{M}$$

where $\mathbf{M} = \mathbf{B}^{-1}$. In this way, the data matrix has been factored into an $n \times n$ matrix **M** and an $m \times n$ matrix **H**. The matrix **M** may be associated with the molecular

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Table I. ^{13}C NMR Chemical Shifts

halide (no.)	position	chemical shifts[a,b]				differential chemical shifts[c]			
		F	Cl	Br	I	F	Cl	Br	I
methyl (1)	α	71.57	25.56	9.64	−24.04	73.67	27.66	11.74	−21.94
ethyl (2)	α	80.01	39.95	27.48	−1.63	73.50	33.34	20.97	−8.14
	β	15.82	18.65	19.11	20.39	9.31	12.14	12.60	13.88
1-propyl (3)	α	85.18	46.59	35.42	8.95	69.05	30.46	19.29	−7.18
	β	23.62	25.95	26.10	26.80	7.32	9.65	9.80	10.50
	γ	9.20	11.34	12.70	15.16	−6.93	−4.79	−3.43	−0.97
2-propyl (4)	α	87.29	53.61	44.76	20.78	70.99	37.31	28.46	4.48
	β	22.61	27.07	28.33	31.07	6.48	10.94	12.20	14.94
1-butyl (5)	α	83.63	44.45	33.14	6.34	70.08	30.90	19.59	−7.21
	β	32.39	34.56	34.68	35.36	7.57	9.74	9.86	10.54
	γ	18.31	19.90	21.15	23.43	−6.51	−4.98	−3.67	−1.39
	δ	13.40	13.02	12.90	12.73	−0.15	−0.53	−0.65	−0.82
tert-butyl (6)	α	93.50	66.89	62.20	43.03	70.20	43.59	38.90	19.73
	β	28.34	34.32	36.31	40.40	3.73	9.71	11.70	15.79
3-pentyl (7)	α	96.48	67.06	61.78	43.90	62.30	32.88	27.60	9.72
	β	27.55	30.98	31.65	33.22	5.22	8.65	9.32	10.89
	γ	9.05	10.70	11.84	13.89	−4.82	−3.17	−2.03	0.02
3-ethyl-3-pentyl (8)	α	99.18	79.47	80.66	71.57	56.93	37.22	38.41	29.32
	β	28.51	32.82	34.08	36.70	3.32	7.63	8.89	11.51
	γ	7.34	8.48	9.51	11.30	−3.52	−2.38	−1.35	0.44
cyclobutyl[d] (9)	1	89.49	52.32	42.34	15.78	67.09	29.92	19.94	−6.62
	2, 4	31.10	34.75	35.46	36.87	8.70	12.35	13.06	14.47
	3	10.54	16.33	18.84	22.94	−11.86	−6.07	−3.56	0.54
cyclopentyl (10)	1	96.54	61.81	53.13	28.18	70.73	36.00	27.32	2.37
	2, 5	33.44	36.91	37.71	39.58	7.63	11.10	11.90	13.77
	3, 4	23.09	22.80	23.06	23.70	−2.72	−3.01	−2.75	−2.11
cyclohexyl (11)	1	90.99	59.90	53.03	32.17	64.04	32.95	26.08	5.22
	2, 6	32.21	36.54	37.38	39.38	5.26	9.59	10.43	12.43
	3, 5	22.68	24.66	25.61	27.03	−4.27	−2.29	−1.34	0.08
	4	25.14	25.01	24.98	25.04	−1.81	−1.94	−1.97	−1.91
exo-2-norbornyl (12)	1	41.84	46.08	46.35	47.89	5.31	9.55	9.82	11.36
	2	95.78	62.30	53.66	29.91	65.92	32.44	23.80	0.05
	3	39.75	43.64	43.75	45.14	9.89	13.78	13.89	15.28
	4	34.42	36.57	36.90	37.91	−2.11	0.04	0.37	1.38
	5	27.87	28.17	27.97	(28.68)	−1.99	−1.69	−1.89	(−1.18)
	6	22.17	26.77	27.39	(28.37)	−7.69	−3.09	−2.47	(−1.49)
	7	34.70	35.09	35.34	36.24	−3.82	−3.43	−3.18	−2.28
7-norbornyl (13)	1, 4	38.43	42.26	42.66	43.88	1.90	5.73	6.13	7.35
	2, 3 (syn)	26.52	26.71	(27.33)	28.28	−3.35	−3.15	(−2.53)	−1.58
	5, 6 (anti)	25.18	27.35	(27.26)	26.90	−4.68	−2.50	(−2.60)	−2.96
	7	99.24	66.29	58.30	35.63	60.72	27.77	19.78	−2.89
1-bicyclo[2.2.2]octyl (14)	1	93.81	67.59	64.73	47.24	69.90	43.68	40.82	23.33
	2, 6	31.04	36.03	37.37	40.28	5.10	10.09	11.43	14.34
	3, 5	27.15	28.00	28.88	29.58	1.21	2.06	2.94	3.64
	4	23.98	22.98	22.39	21.20	0.07	−0.93	−1.52	−2.71
1-bicyclo[3.3.1]nonyl[e] (15)	1	97.72	70.65	69.61	55.44	64.32	42.25	41.21	27.04
	2, 8	37.34	42.12	43.55	46.93	5.36	10.14	11.57	14.95
	3, 7	23.26	24.37	25.35	26.39	0.25	1.36	2.34	3.38
	4, 6	30.48	29.57	29.57	29.51	−1.50	−2.41	−2.41	−2.47
	5	33.47	32.89	33.41	33.28	5.07	4.49	5.01	4.88
	9	41.50	46.02	47.12	50.18	6.08	10.60	11.70	14.76
1-adamantyl[f] (16)	α	90.79	67.25	64.42	48.30	62.04	38.50	35.67	19.55
	β	43.37	48.19	49.71	52.75	5.13	9.95	11.47	14.51
	γ	31.82	32.02	32.85	33.30	3.07	3.27	4.10	4.55
	δ	36.55	36.22	36.17	36.23	−1.69	−2.02	−2.07	−2.01
2-adamantyl[f] (17)	1, 3 (β)	33.36	36.04	36.54	37.80	4.61	7.29	7.79	9.05
	2 (α)	94.60	66.85	62.13	44.62	56.36	28.61	23.89	6.38
	γ (syn)	31.95	31.34	31.96	33.41	−6.29	−6.90	−6.28	−4.83
	γ (anti)	36.27	38.49	38.99	39.23	−1.97	0.25	0.75	0.99
	δ (syn)	27.42	27.36	27.34	27.65	−1.33	−1.39	−1.41	−1.10
	δ (anti)	27.76	27.88	27.95	28.24	−0.99	−0.87	−0.80	−0.51
	ε	37.83	38.13	38.25	38.67	−0.41	−0.11	0.01	0.43
7,7-dimethyl-*exo*-2-norbornyl (18)	1		(52.04)	52.10	52.61		8.11	*g*	8.75
	2		(62.35)	52.26	25.41		32.89	*g*	−4.05
	3		42.91	43.11	43.96		13.45	13.65	−14.50
	4		45.10	45.43	45.54		1.24	1.57	1.68
	5		(28.21)	(29.23)	(30.57)		*g*	*g*	*g*
	6		(26.88)	(26.77)	(26.80)		*g*	*g*	*g*
	7		46.26	46.47	46.85		0.22	0.43	0.81
	syn-CH_3		(22.10)	(22.14)	(22.38)		*g*	*g*	*g*
	anti-CH_3		(22.03)	(22.00)	(22.06)		*g*	*g*	*g*

[a] In parts per million from internal Me_4Si. [b] Values in parentheses may be reversed. [c] $\Delta\delta = \delta_C^{RX} - \delta_C^{RH}$; negative values indicate upfield shifts from the parent hydrocarbon. [d] Reference 40. [e] Reference 43. [f] Reference 44. [g] Value not computed since shift may be reversed.

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

	chemical shifts[a]			
compd (no.)	C(1)	C(2)	C(3)	other
methane[b] (1)	−2.1			
ethane (2)	6.51			
propane (3, 4)	16.13	16.30		
butane (5)	13.55	24.82		
2-methylpropane (6)	24.61	23.30		
pentane (7)	13.87	22.33	34.18	
3-ethylpentane (8)	10.86	25.19	42.25	
cyclobutane[c] (9)	22.4			
cyclopentane (10)	25.81			
cyclohexane (11)	26.95			
norbornane (12, 13)	36.53	29.86		38.52 (C_7)
7,7-dimethylnorbornane (18)	43.86	29.46		46.04 (C_7), 21.20 (CH_3)
bicyclo[2.2.2]octane (14)	23.91	25.94		
1-bicyclo[3.3.1]nonyl[d] (15)	28.40	31.98	23.01	35.42 (C_9)
adamantane (16, 17)	28.75	38.24		

[a] In parts per million from internal Me_4Si. [b] Reference 7. [c] Reference 40. [d] Reference 43.

Table III. Results of Factor Analysis

				rms error, ppm[d]	
data set	positions	n[b]	range,[b] ppm	f[c] = 2	f = 3
all positions	α	17	95.90	1.39	0.77
	β	18	23.48	0.26	0.15
	γ	18	27.14	0.31	0.13
	δ	8	3.73	0.11	0.02
	ε	1	0.84	0.07	0.02
	all	62		0.76	0.42
α	α	17	95.90	0.41	0.11
β, γ, δ, ε	β	18	23.48	0.27	0.11
	γ	18	27.14	0.29	0.11
	δ	8	3.73	0.11	0.03
	ε	1	0.84	0.06	0.02
	β, γ, δ, ε	45		0.26	0.10

[a] Number of carbons of the specified type in the data set. [b] Range of chemical shifts for the specified carbon type. [c] Number of factors used in fitting the data. [d] For $f = 4$ the root-mean-square error was zero in all cases.

positions, and the matrix **H** may be associated with the substituents.[46]

The input data may be exactly reproduced by taking the product of **H** and **M**. However, it may also be reproduced, although with some, usually small, error by smaller matrices formed by deleting rows from **M** and columns from **H**. The eigenvalues, λ, indicate the relative importance of the rows in **M** and provide a guide to how many rows may be eliminated without leading to large errors.[46] The number of rows which are retained correspond to the number of independent factors which are needed in order to reproduce the experimental data within a given error limit.

In the present case, an analysis of the data for 62 sets of halogen-induced differential chemical shifts from Table I (1–17; X = F, Cl, Br, I) indicated that there were two major substituent factors having λ = 37 and 7, respectively, as well as a smaller third factor with λ = 0.3. The other λ's were vanishingly small. If two substituent factors are used, the differential chemical shifts are given by eq 3, and

$$\Delta\delta_{xi} = h_{x1}m_{1i} + h_{x2}m_{2i} \tag{3}$$

with three factors they are given by eq 4, where i indicates

$$\Delta\delta_{xi} = h_{x1}m_{1i} + h_{x2}m_{2i} + h_{x3}m_{3i} \tag{4}$$

the molecular position, x indicates the halogen used, h_{xk} represents the elements of the **H** matrix, and m_{ki} represents the elements of the **M** matrix. It can be seen that the final result of factor analysis is a set of equations similar to those obtained via a regression analysis. However, in factor analysis one does not bias the result by a priori assumptions. In these terms, *the factor analysis corresponds to a regression analysis in which the independent variables are not predetermined.*

By use of eq 3, the experimental data are reproduced with a root-mean-square error of 0.76 ppm, whereas with eq 4, the root-mean-square error is reduced to 0.42 ppm. The largest deviations were found at the α-positions. When the α-positions were treated separately, they gave slightly different **M** and **H** matrices, and the use of three factors (eq 4) gave a root-mean-square error of 0.11 ppm. The β, γ, δ, and ε positions when treated as a group gave a root-mean-square error of 0.10 ppm. The results are detailed in Table III.

It can be seen from Table III that three substituent factors will reproduce the experimental error. The use of four factors reduces the error to zero, but it is clearly inappropriate to include a factor which reduces the error to less than that of the experiment. Two substituent factors lead to a larger deviation between the calculated and experimental chemical shifts, suggesting that the third factor has some small significance.

It may be concluded that only three independent substituent factors are needed to fit the experimental data within the experimental error. It is possible that any factor may involve several physical quantities characteristic of the substituent. However, should this be the case, the same linear combination of these factors is appropriate for all of the data. Thus, these physical quantities would not be independent variables in this case.

Factor analysis, by itself, does not give information concerning the nature of the independent substituent factors which are responsible for the correlation. However, a matrix may be subjected to an orthogonal transformation without changing its values. This is equivalent to rotating the matrix in space. When both the **M** and **H** matrices are subjected to the same orthogonal transformation, the product will still reproduce **D**, and such rotation of the matrices will often yield representations in which the nature of the factors becomes apparent.

Trial rotations of the two-factor, truncated, halogen-substituent matrix suggested that the two principal halogen-property vectors were approximately a constant term and one which increases linearly on going from fluorine

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[46] (a) Weiner, P. H.; Malinowski, E. R.; Levinstone, A. R. *J. Phys. Chem.* **1970**, *74*, 4537. (b) Weiner, P. H.; Howrey, D. H. *Anal. Chem.* **1972**, *44*, 1189.

Table IV. Halogen Substituent Parameters from Factor Analysis

		rotated halogen property vectors				
		two-factor solution		three-factor solution		
halogen	test vectors	a_1	a_2	a_1	a_2	a_3
		A. α Positions[a]				
F	1.0 1.0 1.0	1.037	0.991	0.995	1.001	0.973
Cl	1.0 2.0 0.0	0.895	2.021	0.996	2.005	−0.194
Br	1.0 3.0 0.0	1.040	2.996	1.060	2.992	0.341
I	1.0 4.0 1.0	1.014	3.994	0.974	4.004	0.849
		rms error 0.41			rms error 0.11	
		B. β, γ, δ, and ε Positions[b]				
F	1.0 1.0 1.0	0.976	0.795	1.000	0.988	1.008
Cl	1.0 2.0 0.0	1.030	2.428	0.997	2.164	−0.106
Br	1.0 3.0 0.0	1.022	2.936	1.004	2.789	0.137
I	1.0 4.0 1.0	0.969	3.820	0.999	4.061	0.961
		rms error 0.26			rms error 0.10	

[a] Eigenvalues: $\lambda_1 = 16.3, \lambda_2 = 0.65, \lambda_3 = 0.002, \lambda_4 = 0.0002$. [b] Eigenvalues: $\lambda_1 = 37.4, \lambda_2 = 7.3, \lambda_3 = 0.3, \lambda_4 = 0.03$.

to iodine as the substituent. In the two-factor case, the trial matrix for **H** was then taken as **H′**. Rotation of the

$$\begin{vmatrix} 1 & 1 \\ 1 & 2 \\ 1 & 3 \\ 1 & 4 \end{vmatrix} = H'$$

truncated (4 × 2) original H matrix to give the "best" fit to the trial matrix gave the results shown in Table IV. A corresponding rotation of the truncated (2 × n) **M** matrix gave a set of vectors which may be used to study the structural dependence of the substituent effects, and these are given in Table V. With two factors, the calculated differential chemical shifts are given by eq 5, where a_{xk}

$$\Delta\delta_{xi} = a_{x1}b_{1i} + a_{x2}b_{2i} \qquad (5)$$

represents the elements of the rotated **H** matrix (Table IV) and b_{ki} represents the elements of the rotated **M** matrix (Table V).

When three halogen factors were used, the third factor was not well-defined, as might be expected from the small λ associated with it. Any trial vector which introduced curvature was satisfactory. Thus, 1,2,4,8 or 1,0,0,1 could equally well be used. The latter was chosen since it would lead to b_{2i} terms close to those obtained in the two factor case. The trial matrix for **H** was then taken as **H′**. Ro-

$$\begin{vmatrix} 1 & 1 & 1 \\ 1 & 2 & 0 \\ 1 & 3 & 0 \\ 1 & 4 & 1 \end{vmatrix} = H'$$

tation of the truncated (4 × 3) original **H** matrix gave the results shown in Table IV, and a corresponding rotation of the truncated (3 × n) **M** matrix gave the results listed in Table V. With three factors, the calculated differential chemical shifts are given by eq 6, where the three-factor

$$\Delta\delta_{xi} = a_{x1}b_{1i} + a_{x2}b_{2i} + a_{x3}b_{3i} \qquad (6)$$

halogen parameters (a_{xk}) are given in Table IV and the molecular sensitivity factors (b_{ki}) are listed in Table V.

The nature of the general results of this analysis is best appreciated by examination of eq 5 and 6 and the halogen-substituent parameters listed in Table IV. It is to be noted that the a_1 terms are essentially unity for all the halogens, and the a_2 factors for F, Cl, Br, and I approximate a linear progression, i.e., 1, 2, 3, 4. Thus the two-factor result (eq 5) reduces in practice to linear correlation of Δδ with the a_2 factors: the b_1 values correspond to intercepts and the b_2 values to slopes. Insofar as the b_3 factors are small (particularly for positions removed from the α-carbon), the factor analysis indicates that, to a good approximation, the differential chemical shifts for a series of monosubstituted alkyl halides may be linearly correlated with an arithmetic series.[47]

Discussion

Having established that the ^{13}C chemical shifts of acyclic and alicyclic halides may be reduced to a three-factor problem, we wish to see what may be deduced from the result. The two main questions are as follows. (1) What is the physical significance of the three independent halogen substituent parameters (a values)? (2) What determines the values of the molecular parameters (b values) which reflect the sensitivity of a given molecular position to the three-substituent effects? It should be noted that since the factor analysis involved no assumptions concerning the origin of ^{13}C shielding, the results of the analysis are not a priori supportive of any particular model or mechanism.

The first halogen substituent factor, a_1, is essentially a constant for all halogens. As a result, factor analysis has reduced the problem to a plot of differential chemical shifts against the a_2 factors, leading to a slope (b_2), an intercept (b_1), and a small curvature term (b_3).

The substituent parameter which is most characteristic of the halogens is a_2. The corresponding b_2 values correspond to the slopes of the plots and are a measure of the sensitivity of a given carbon to the change in substituents going from F to I. A consistency in both sign and magnitude of these sensitivity factors for nuclei at a given number of bonds from the substituent is apparent from the b_2 values in Table V: the α-carbons have the largest b_2 terms and these are invariably of negative sign (−26.5 ± 2.1 for primary halides, −19.9 ± 2.1 for secondary halides, and −12.8 ± 2.2 for tertiary halides), the β nuclei are characterized by smaller b_2's of positive sign (1.1 ± 0.2 for primary halides, 1.9 ± 0.3 for secondary halides, and 3.1 ± 0.3 for tertiary halides), the γ-positions have generally positive b_2 values of similar magnitude (2.0 ± 2.0), and the

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[47] Such a linear correlation is of interest in its own right as a guide to spectral assignment. A plot of the ^{13}C chemical shifts of a given carbon for the series of halides vs. the integers 1–4 will give a reasonably straight line if the assignments are correct. The largest deviations from linearity will be found when analyzing α-carbon shifts since this position has the largest values for b_3.

Table V

	two-factor solution			three-factor solution			
molecule (no.)	b_1	b_2	rms error	b_1	b_2	b_3	rms error
			Molecular Sensitivity Factors for α-Carbons				
methyl (1)	100.85	−31.08	0.12	94.49	−30.73	10.65	0.05
ethyl (2)	96.43	−26.47	0.33	90.64	−26.15	9.70	0.09
1-propyl (3)	89.87	−24.72	0.23	84.04	−24.39	10.06	0.13
2-propyl (4)	89.53	−21.50	0.47	84.23	−21.22	8.59	0.16
1-butyl (5)	91.35	−25.07	0.25	85.23	−24.73	10.25	0.15
tert-butyl (6)	83.84	−16.19	0.78	79.59	−15.95	7.13	0.07
3-pentyl (7)	75.81	−16.96	0.57	70.31	−16.65	9.21	0.14
3-ethyl-3-pentyl (8)	62.56	−8.73	0.82	57.65	−8.46	8.23	0.08
cyclobutyl (9)	87.50	−23.83	0.21	81.89	−23.52	9.40	0.21
cyclopentyl (10)	89.59	−22.07	0.33	84.31	−21.78	8.85	0.07
cyclohexyl (11)	79.82	−18.98	0.10	74.64	−18.70	8.69	0.02
2-norbornyl (12)	84.07	−21.29	0.18	78.93	−21.00	8.61	0.03
7-norbornyl (13)	78.02	−20.55	0.29	72.74	−20.26	8.85	0.18
1-bicyclo[2.2.2]octyl (14)	81.91	−14.87	0.31	77.18	−14.61	7.92	0.05
1-bicyclo[3.3.1]nonyl (15)	73.58	−11.85	0.24	69.31	−11.61	7.15	0.05
1-adamantyl (16)	73.14	−13.58	0.37	69.02	−13.35	6.89	0.09
2-adamantyl (17)	69.30	−16.08	0.53	64.24	−15.80	8.47	0.13
			Molecular Sensitivity Factors for β-Carbons				
ethyl (2)	8.23	1.51	0.14	8.78	1.46	−0.91	0.11
1-propyl (3)	6.87	1.05	0.12	7.26	1.01	−0.93	0.11
2-propyl (4)	4.04	2.78	0.21	4.85	2.72	−1.05	0.08
1-butyl (5)	6.98	0.98	0.12	7.50	0.94	−0.85	0.12
tert-butyl (6)	0.35	3.96	0.29	1.08	3.90	−1.19	0.06
3-pentyl (7)	3.85	1.87	0.09	4.51	1.82	−1.08	0.09
3-ethyl-3-pentyl (8)	1.11	2.70	0.11	1.74	2.64	−1.02	0.06
cyclobutyl (9)	7.38	1.91	0.07	8.15	1.85	−1.27	0.07
cyclopentyl (10)	6.06	2.02	0.16	6.65	1.97	−0.95	0.09
cyclohexyl (11)	3.53	2.36	0.12	4.36	2.30	−1.35	0.11
2-norbornyl (12) C(1)	4.06	1.99	0.31	5.01	1.91	−1.56	0.21
C(3)	8.81	1.77	0.26	9.70	1.69	−1.45	0.24
7-norbornyl (13)	0.78	1.81	0.34	1.69	1.73	−1.47	0.12
1-bicyclo[2.2.2]octyl (14)	2.67	3.04	0.15	3.43	2.97	−1.25	0.09
1-bicyclo[3.3.1]nonyl (15) C(2, 8)	2.68	3.14	0.33	3.24	3.09	−0.91	0.11
C(9)	3.72	2.83	0.30	4.30	2.78	−0.95	0.16
1-adamantyl (16)	2.57	3.08	0.22	3.23	3.03	−1.08	0.05
2-adamantyl (17)	3.54	1.46	0.08	4.05	1.42	−0.83	0.08
			Molecular Sensitivity Factors for γ-Carbons				
1-propyl (3)	−9.07	1.95	0.24	−8.95	1.95	−0.08	0.07
1-butyl (5)	−8.31	1.67	0.33	−8.51	1.68	0.33	0.08
3-pentyl (7)	−6.45	1.58	0.26	−6.53	1.59	0.14	0.06
3-ethyl-3-pentyl (8)	−4.93	1.29	0.31	−5.10	1.30	0.29	0.07
cyclobutyl (9)	−15.44	4.09	0.13	−14.81	4.03	−1.04	0.12
cyclopentyl (10)	−3.11	0.18	0.19	−3.40	2.07	0.47	0.01
cyclohexyl (11)	−5.54	1.44	0.07	−5.33	1.42	−0.34	0.06
2-norbornyl (12) C(4)	−2.94	1.15	0.25	−2.53	1.11	−0.67	0.06
C(6)	−8.86	2.08	0.76	−7.64	1.98	−1.98	0.02
C(7)	−4.40	0.49	0.11	−4.53	0.50	0.22	0.07
7-norbornyl (13) γ-(syn)	−4.09	0.57	0.22	−4.32	0.59	0.38	0.02
γ-(anti)	−4.67	0.60	0.66	−3.84	0.53	−1.35	0.03
1-bicyclo[2.2.2]octyl (14)	0.43	0.82	0.21	0.47	0.81	−0.06	0.14
1-bicyclo[3.3.1]nonyl (15) C(5)	4.97	−0.04	0.31	4.78	−0.03	0.29	0.16
C(3, 7)	−0.77	1.04	0.23	−0.74	1.04	−0.04	0.12
1-adamantyl (16)	2.48	0.51	0.31	2.38	0.51	0.17	0.16
2-adamantyl (17) γ(syn)	−7.19	0.44	0.43	−7.83	0.49	1.05	0.04
γ(anti)	−2.51	1.01	0.37	−1.86	0.96	−1.05	0.06
			Molecular Sensitivity Factors for δ- and ε-Carbons				
1-butyl (5)	0.02	−0.22	0.01	−0.05	−0.22	0.12	0.00
cyclohexyl (11)	−1.82	−0.04	0.01	−1.88	−0.03	0.09	0.01
2-norbornyl (12)	−2.27	0.23	0.15	−2.37	0.24	0.15	0.14
1-bicyclo[2.2.2]octyl (14)	0.99	−0.91	0.20	1.02	−0.91	−0.05	0.01
1-bicyclo[3.3.1]nonyl (15)	−1.39	−0.33	0.13	−1.67	−0.30	0.46	0.03
1-adamantyl (16)	−1.67	−0.11	0.03	−1.79	−0.10	0.20	0.01
2-adamantyl (17) δ(syn)	−1.47	0.06	0.07	−1.57	0.07	0.17	0.04
δ(anti)	−1.17	0.15	0.04	−1.22	0.15	0.07	0.01
ε	−0.69	0.27	0.06	−0.72	0.27	0.04	0.02

δ- and ε-carbons show the smallest b_2 factors, and these are of variable sign. Thus, the β- and γ-positions are invariably shifted to lower field when the halogen is changed from F to I while the α-carbon and several of the δ and ε nuclei move to higher field as the "hard" fluorine substituent is replaced by "softer" halogens.

The observed effects have a superficial resemblance to the operation of magnetic anisotropy.[48] Thus, when the

Table VI. Factor Analysis Applied to Non-NMR Halogen Properties

	F		Cl		Br		I	
property	obsd	calcd[e]	obsd	calcd	obsd	calcd	obsd	calcd
1/IP, methyl halides, $ev^{-1} \times 10^2$ [a]	7.81	7.88	8.87	8.81	9.50	9.41	10.48	10.56
first electron transition, methyl halides, nm $\times 10^{-2}$ [b]	1.33	1.30	1.73	1.75	2.02	2.05	2.58	2.56
longitudinal bond polarizabilities, $cm^3 \times 10^{24}$ [c]	1.20	1.22	3.80	3.72	5.30	5.38	8.10	8.08
transverse bond polarizabilities, $cm^3 \times 10^{24}$ [c]	0.40	0.40	1.80	1.79	2.70	2.71	4.20	4.20
atomic contribution to molar diamagnetic susceptibility, $\times 10^5$ [d]	−0.64	−0.64	−1.99	−2.04	−3.04	−2.97	−4.46	−4.48

[a] Reference 50. [b] Reference 51. [c] Reference 52. [d] Reference 53. [e] Based on a two-parameter fit. The rotated halogen property matrix elements were 1.004, 0.998, 0.992, 1.005 and 0.992, 2.106, 2.845, 4.056.

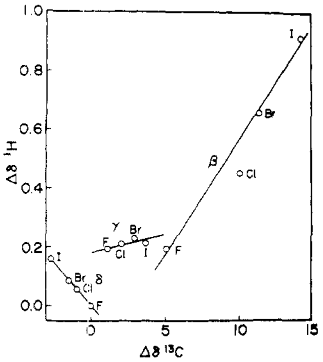

Figure 2. Relation between ^{1}H and ^{13}C chemical shifts for 1-halobicyclo[2.2.2]octanes (14) in parts per million from internal Me_4Si.

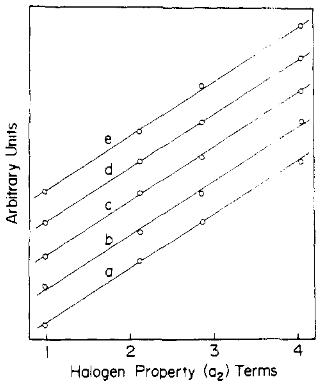

Figure 3. Correlation between non-NMR physical parameters for the halogens and the halogen substituent (a_2) terms derived from the three-factor analysis for the β-ϵ positions (Table IV). The parameters, scaled to a common slope for convenience in presentation, are (a) 1/IP for the methyl halides, (b) wavelength of the first electronic transition of the methyl halides, (c) longitudinal bond polarizabilities, (d) transverse bond polarizabilities, and (e) atomic contributions to the molar diamagnetic susceptibility.

δ position is collinear with the C–X bond, as with the 1-halobicyclo[2.2.2]octanes (14), the sign of b_2 is negative, as it is with the α-carbon [$b_2(\alpha) = -14.6$, $b_2(\delta) = -0.91$], and the ratio of the magnitudes of the b_2's is close to the ratio of R^{-3} values where the R's are the distance from the halogen to the α- and δ-carbons, respectively. When the carbon is moved away from a collinear relationship, as with the β- and γ-carbons, and the δ-cabons are in a chair cyclohexane conformation, the sign of b_2 has the opposite sign from that found at the α-position.

However, such a simple explanation cannot be correct. We have previously shown that carbon and hydrogen chemical shifts are frequently related.[1] Such a relationship is examined for the 1-halobicyclo[2.2.2]octanes (14) in Figure 2. The shifts are fairly well correlated at each of the β-, γ-, and δ-positions. If magnetic anisotropy of the halogen substituent were dominant, a relation between the ^{1}H and ^{13}C chemical shifts would be expected with positive slopes somewhat less than unity since the distance from the halogen to the hydrogen would be greater than that to the corresponding carbon. At the β-position, the slope is +0.07. The sign is correct, but the magnitude is much too small. The slope at the γ-position is close to zero, and at the δ-position it is −0.06. Here, the sign is negative. The maximum slope for plots of this sort appears to be on the order of the ratio of the ranges of ^{1}H and ^{13}C chemical shifts.

In order to gain more information concerning the mechanism(s) which operates in producing the above slopes, we have examined the halogen substituent parameters, a_2. We have noted that a number of properties of halogen-containing molecules have trends which appeared to be related to the a_2's.[49] Among the *non-NMR parameters* linearly related to a_2 (Figure 3) are the reciprocal of the ionization potentials of the methyl halides,[50] the wavelength of the first electronic transition of the methyl halides,[51] the longitudinal and transverse C–X bond polarizabilities,[52] and the atomic contribution to the molar diamagnetic susceptibility[53] (halogen electronegativity is

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(48) Magnetic anisotropy (McConnell, H. M. *J. Chem. Phys.* **1957**, *27*, 226. Pople, J. A. *Proc. R. Soc. London, Ser. A* **1975**, *239*, 550) has an angular dependence which could lead to a different sign at the α- and β-positions as well as an inverse third power dependence on the distance between the substituent and the position being examined.

(49) At the inception of this study and prior to factor analysis, the empirical *Q parameter* introduced by Schaefer and co-workers was used in an attempt to correlate the $\Delta\delta$ values in Table I [see: Hiruska, F.; Hutton, H. M.; Schaefer, T. *Can. J. Chem.* **1975**, *43*, 2392]. This parameter, which is given by $Q = P/Ir^3$ where P is the polarizability of the C–X bond, I is the first ionization potential of the atom X_1 and r is the C–X bond length, has values as given by Schaefer which are roughly an arithmetic progression for the carbon–halogen bonds (F, Cl, Br, I): 1.04, 2.55, 3.16 and 3.98, respectively. In a later paper, Schaefer noted that Q was itself nearly linearly related to the ionization potential of X since P/r^3 is not a large factor [Schaefer, T.; Hruska, F.; Hutton, H. M. *Can. J. Chem.* **1967**, *45*, 3143]. The initial observation of a rough correlation between Q and $\Delta\delta$ led to the use of an arithmetic progression as a test vector for factor analysis.

(50) The adiabatic ionization potentials of the methyl halides (F, Cl, Br, I) are 12.80, 11.28, 10.53, and 9.54 eV, respectively. These and other ionization potentials of alkyl halides have been found to be linearly related to the inductive substituent constants σ_I and the polar substituent constants σ^*. *Cf.*: Levitt, L. S.; Levitt, B. W. *Tetrahedron* **1973**, *29*, 941; Levitt, L. S.; Widing, H. F. *Prog. Phys. Org. Chem.* **1976**, *12*, 119.

(51) The first electronic transitions of the methyl halides (F, Cl, Br, I) are 133, 173, 202, and 258 nm, respectively.[34a]

(52) The longitudinal bond polarizabilities of the carbon–halogen bonds (F, Cl, Br, I) are 1.20 × 10^{-24}, 3.80 × 10^{-24}, 5.30 × 10^{-24}, and 8.10 × 10^{-24} cm^3, respectively. The corresponding transverse polarizabilities are 0.40 × 10^{-24}, 1.80 × 10^{-24}, 2.70 × 10^{-24}, and 4.20 × 10^{-24} cm^3 [Le Fevre, R. J. *Adv. Phys. Org. Chem.* **1965**, *3*, 50].

conspicuously absent from this list[54]). Factor analysis using these non-NMR parameters (Table VI) reproduces the experimental values and leads to two halogen vectors which are essentially identical with the substituent parameters for the β-, γ-, δ-, and ϵ-positions (Table IV). The a_2 terms (and the parameters listed above) also appear to be linearly related to fundamental *magnetic* properties of C–X bonds, including the net longitudinal and transverse magnetic susceptibilities ($\chi_\parallel$ and $\chi_\perp$)[55] as well as their diamagnetic[55] and paramagnetic[56] components. These remarkably good linear correlations strongly suggest that many other physical and spectroscopic properties of halogen-containing molecules will be linearly related to changes in the ^{13}C chemical shifts of the halides since many bulk properties are linearly controlled by just those parameters to which a_2 is linearly related. We are currently investigating the obvious consequences of such correlations.

While it is possible that the linear relationships among all of these quantities might be accidental, this seems highly unlikely. We are, however, unaware of any theory which has successfully related all of the properties of C–X bonds and accounted for the apparent linearity of the correlations. The one common feature of the C–X bond parameters noted above would appear to be the "freeness" of the valence electrons at or about the halogen. In these terms, the intrinsic substituent effects controlling changes in ^{13}C shielding at all molecular positions as the halogen is varied are due to the relative ease with which the electrons about halogen may be perturbed. The fact that alkyl substitution at the α-carbon changes the sensitivity (b_2 factors) of ^{13}C nuclei to the a_2 substituent effect is consistent with this interpretation. Levitt,[50] for example, has demonstrated that the ionization potentials of alkyl halides vary linearly with alkyl group inductive substituent parameters: an increase in the number of alkyl groups at C(α) results in a decrease in IP.

It is not surprising that the a_2 terms are related to the reciprocals of the ionization potentials of the alkyl halides. The paramagnetic contribution to the chemical shift is generally acknowledged to be dominant for ^{13}C nuclei, and in the Karplus–Pople treatment[18,21] it is inversely proportional to the mean excitation energy. The latter may be approximated by the ionization potential. Corrections to the screening due to the magnetic susceptibility of the C–X bond should also be correlated with the a_2 terms since they are related to both the paramagnetic and diamagnetic susceptibilities of the bonds. Thus, the linear dependence of ^{13}C shifts for a series of halides on only one set of halogen substituent parameters is not surprising in view of the linear relationship between the a_2 parameters and all-important C–X bond properties. The origin of the apparent directional characteristics of the b_2 terms are not at all clear at this time.

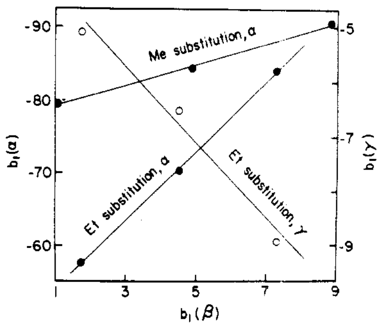

Figure 4. Correlation of the b_1 (intercept) values for the α and γ positions with those at the β position. The methyl substitution series is ethyl (**2**), 2-propyl (**4**), and *tert*-butyl (**6**) halides. The ethyl substitution series is 1-propyl (**3**), 3-pentyl (**7**), and 3-ethyl-3-pentyl (**8**) halides.

The other important halogen substituent factor, a_1, is essentially a constant for all halogens. Since the chemical shift is known to be dependent on the electron density distribution, the intercept may reasonably be ascribed to the polar effect of the halogens. As indicated above, the polar effect should be roughly constant beyond the α-position. The b_1 terms would thus be a measure of the sensitivity of a particular position to the polar effect of halogen.

An examination of the b_1 values in Table V reveals a remarkable consistency in both sign and magnitude for factors associated with nuclei a given number of bonds from the substituent. The α-carbons have large and positive b_1's (76 ± 19), the β-positions show smaller positive values (2.5 ± 1.5), the γ nuclei generally have negative b_1 factors (−15 to −2) with the exception of those molecules (**14–16**) having the halogen at the bridgehead position, and the δ- and ϵ-positions are characterized by small b_1's of variable sign. Here, a positive value of b_1 indicates that the nucleus is deshielded relative to the hydrocarbons by the first halogen substituent factor, and a negative b_1 corresponds to shielding of that position via the operation of a_1.

It is interesting to examine the effect of alkyl substitution on the magnitudes of the b_1 terms. If one compares the b_1 values for the α-carbons of methyl (**1**), ethyl (**2**), 2-propyl (**4**), and *tert*-butyl (**6**) halides (94.5, 40.5, 84.2, and 75.6 ppm, respectively), the magnitudes are seen to decrease monotonically in response to the opposing polar effect of the methyl substituents. An analogous trend is found for the b_1 values at the β-carbons in these molecules [$b_1(\beta)$ = 8.78, 4.85, and 1.08 for compounds **2**, **4**, and **6**, respectively]. A similar trend is found in a series of compounds which differ in the number of ethyl groups attached to the α-carbon [1-propyl (**3**), 3-pentyl (**7**), and 3-ethyl-3-pentyl (**8**) halides]. In each case, the b_1 values for the α- and β-carbons decrease in magnitude as the number of electron-donating alkyl groups at the α-position is increased.

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(53) The atomic contributions to the molar diamagnetic susceptibility (F, Cl, Br, I) are -0.64×10^{-5}, -1.99×10^{-5}, -3.04×10^{-5}, and -4.46×10^{-5} esu mol^{-1}, respectively. Pascal, P. "Chimie Generale"; Mason et Cie: Paris, 1949.

(54) Although the literature is replete with attempted correlations of ^{13}C chemical shifts with substituent electronegativity (cf. ref 12, 20–22, and 35), the correlations are, at best, suggestive of a trend $\Delta\delta$ with changes in electronegativity. As noted in the body of the paper, the fundamental halogen properties given in Table VI are not linearly related to this derived parameter.

(55) The net longitudinal magnetic susceptibilities ($\chi_\parallel$) of the methyl halides (F, Cl, Br, I) are -23.3×10^{-6}, -37.3×10^{-6}, -48.5×10^{-6}, and -64.5×10^{-6} erg G^{-2} mol^{-1}, respectively. The corresponding net transverse magnetic susceptibilities ($\chi_\perp$) are -15.1×10^{-6}, -29.4×10^{-6}, -40.0×10^{-6}, and -53.5×10^{-6} erg G^{-2} mol^{-1}, respectively. The diamagnetic component of the longitudinal magnetic susceptibilities ($\chi_\parallel^{d}$) for the methyl halides (F, Cl, Br, I) are -33.1×10^{-6}, -46.9×10^{-6}, -58.3×10^{-6}, and -74.2×10^{-6} erg G^{-2} mol^{-1}, respectively. The diamagnetic component of the transverse susceptibilities ($\chi_\perp^{d}$) of these componds are -71.9×10^{-6}, -129.8×10^{-6}, -178.2×10^{-6}, and -231.2×10^{-6} erg G^{-2} mol^{-1} respectively [Appleman, B. R.; Dailey, B. P. *Adv. Magn. Reson.* **1974**, *7*, 310]. Plots of these values against the three-factor a_2 parameters for the β–ϵ positions (Table IV) gave linear relationships with r between 0.996 and 0.999.

(56) The transverse paramagnetic susceptibilities ($\chi_\perp^{p}$) of the methyl halides (F, Cl, Br, I) are 57.3×10^{-6}, 100.5×10^{-6}, 138.2×10^{-6}, and 177.6×10^{-6} erg G^{-2} mol^{-1} (Appleman and Dailey[55]). A plot of these values against the a_2 values for the β–ϵ positions gave a linear relationship with $r = 0.994$ and a root-mean-square rms error of 5.0×10^{-6} erg G^{-2} mol^{-1}. The longitudinal paramagnetic susceptibilities of the methyl halides are virtually constant ($\chi^{p} = 9.7 \pm 0.1 \times 10^{-6}$ erg G^{-2} mol^{-1}) and would be linearly related to any vector. It is interesting to note that the transverse compound ($\sigma_\perp$) of the shielding tensor for the methyl halides[55] (99, 161, 185, and 244 ppm for F through I, respectively) also are linearly related to the a_2 values ($r = 0.998$). The σ values for the methyl halides are roughly constant.

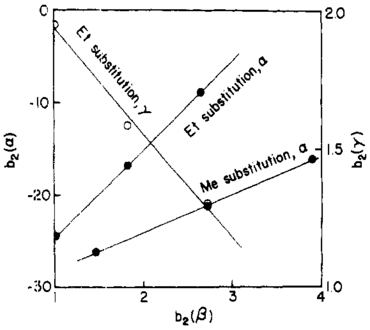

Figure 5. Correlation of the b_2 (slope) values for the α and γ positions with those at the β position. The series are the same as those in Figure 2.

The shielding of the γ-position by the halogen factor, a_1, is reminiscent of the upfield shifts caused by both gauche and anti second-row heteroatom substituents. In an earlier study,[57] the only exceptions to the "γ-anti" effect of second-row heteroatoms were found in systems having the substituent attached to a bridgehead carbon. As noted above, the bridgehead halides **14–16**, are also anomalous in this study in that they have positive b_1 values for the γ-carbons.[58]

Although the magnitudes of the b_1 values for the γ-carbons appear at first glance to be scattered, regular trends are found in the above series having increasing alkyl substitution. In fact, the b_1 values at the α-, β-, and γ-positions are linearly related for these compounds (Figure 4). Remarkably, the same is true for the b_2 values (Figure 5). It is clear from these plots that structural changes affect both b_1 and b_2 values at the α-, β-, and γ-positions in related ways. This suggests that the mechanisms by which the a_1 factors operate at the several positions are strongly related. A similar conclusion is reached for the a_2 factors.

The third substituent factor in the analysis (a_3) is more difficult to interpret than the first two major factors. It seems clear from the analysis the function of a_3 is to introduce curvature into the two-factor results (eq 5), and any test vector which will provide this curvature is a satisfactory candidate.

The signs and magnitudes of the molecular parameters associated with the a_3 factors are again quite dependent on the position of the nucleus relative to the halogen substituent. At the α-position, b_3 terms are large and invariably positive (8.8 ± 1.9), and they seem to decrease monotonically with increasing alkyl substitution at C(α) as do the b_1 and b_2 terms. The b_3 values at β-carbons are negative and smaller in magnitude than those for the α-position (−0.8 ± 0.4), and they seem to become more negative with increasing alkyl substitution at the halogen-bearing carbon. The situation at C(γ) is more complex since b_3 values at this position vary widely in both sign and magnitude (−0.5 ± 1.5). Conformational effects appear to be important since the largest negative values are found for γ-carbon nuclei which are rigidly held anti to the halogen. The small magnitude of b_3 values for δ- and ϵ-nuclei precludes any rational discussion of the effect of a_3 at remote positions.

The *exo*-2-halo-7,7-dimethylnorbornanes (**18**; X = Cl, Br, I) were not included in the factor analysis, but their differential chemical shifts are of some interest in their own right. An examination of the chemical shift data for **18** in Table I reveals that the 7-*syn*- and 7-*anti*-methyl nuclei have very nearly identical shifts in the three halides studied. These molecules were initially prepared to probe the effect of sterically proximate groups separated by four bonds, and the unexpectedly similar shifts found for both *syn*- and *anti*-CH_3's at the δ-position made assignment difficult (see Experimental Section). The concept of a "steric compression" shift, be it upfield or downfield, would not seem to be relevant in this case as noted elsewhere.[1]

Conclusions

The nature of the halogen substituent effects on ^{13}C chemical shifts in aliphatic halides has been investigated by factor analysis. Changes in chemical shift resulting from replacement of a hydrogen by halogen ($\Delta\delta$ values) are separable into two sets of parameters: "intrinsic" substituent factors (a values) characteristic of the halogen and attenuation factors (b values) reflecting the sensitivity of each molecular position to the halogen substituent effects. The results of the analysis reveal that *halogen substituents affect ^{13}C shifts in three independent ways.* The three substituent effects, in order of decreasing importance, have been shown to be (i) a constant term for all halogens (a_1 factor) which is ascribed to the polar effect of halogen vis-à-vis hydrogen, (ii) an effect (a_2 factor) increasing approximately as 1, 2, 3, and 4 for the series F to I which controls differences in $\Delta\delta$ within the halide series and is related to the "freeness" of valence electrons about halogens, and (iii) a considerably less significant parameter (a_3 factor) which is less well-defined than the two major substituent effects and is most important at the α-position.

Each molecular position (α, β, γ, δ, ϵ) is characterized by a sensitivity (b_1, b_2, b_3) to each of the three halogen substituent effects. The structural dependence of the sensitivity factors provides an insight into the mechanism of transmission of each of the three independent halogen effects responsible for the overall effect of halogen on ^{13}C shifts. Analysis of the effect of structural change on the b_1 and b_2 (b_3 values are very small beyond the α-position) sensitivities reveals that the two most important halogen substituent effects, characterized by a_1 and a_2, are each transmitted to the α-, β-, and γ-positions via the same or linearly related mechanisms (Figures 4 and 5).

The change in chemical shift at a nucleus when the halogen is varied from X = F to X = I is determined by the a_2 halogen parameter which increases linearly for the series X = F to X = I. The values of the a_2 terms (Table IV) are linearly related to a variety of properties characteristic of the halides (Figure 3 and Table VI). As far as we are aware, there has been no theoretical treatment which quantitatively relates all of these halogen properties, and, in the absence of this more rigorous understanding, we have suggested that they relate to the "freeness" of the valence electrons about the halogen.

The linear interrelationship among the halogen properties and the a_2 halogen factors is significant in its own right since these fundamental properties of C–X bonds are known to affect the physical, chemical, and spectroscopic behavior of halogen-containing compounds. We note the following obvious consequences of the linear relationships: (1) the observed correlation of ^{13}C and ^1H chemical shifts in ethyl[35] and cyclobutyl halides[1] may well be examples

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[58] It would be interesting to explore b_1 values for γ-carbons in nonbridgehead rigid systems since recent studies have shown that second-row heteroatoms may cause downfield shifts at the γ-*anti*-carbon when the heteroatom is attached to a tertiary center (Wiseman, J. R.; Krabbenhoft, H. D. *J. Org. Chem.* **1977**, *42*, 2240 and references cited therein). A plot of the recently reported ^{13}C shifts for the diastereoisomeric 1-halo-1-methyl-4-*tert*-butylcyclohexanes (Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866) against the a_2 parameters gives b_1 (γ-anti) = +3.6 and b_1 (γ-gauche) = −6.3.

of a more general phenomenon since the diamagnetic and paramagnetic susceptibilities of C–X bonds appear to be linearly related; (2) changes in intermolecular association between RX molecules depend, to a first approximation, on polarizability changes (the C–X bond dipoles are virtually constant for the halide series) with the result that one might reasonably expect good correlation between ^{13}C chemical shifts and the physical, chemical, and spectroscopic properties of RX molecules controlled by polarizability factors. We are actively investigating these possibilities by the factor analysis method.

It will also be of interest to determine whether or not other substituents such as methyl, hydroxy, and cyano may fit the same pattern as found for the halogens. The observation of Roberts et al. that the ^{13}C chemical shifts caused by hydroxy and methyl as substituents were linearly related[59] suggests that the treatment could be extended to these substituents.

Experimental Section

Melting points and boiling points are uncorrected. Proton magnetic resonance spectra were recorded on JEOL MH-100, Perkin-Elmer R32, or Bruker XH-270 instruments, and the shifts are referenced with respect to internal Me_4Si. Carbon-13 magnetic resonance spectra were recorded on either a Varian CFT-20 or a Bruker XH-270 spectrometer in the FT mode operating at 67.88 MHz. Carbon-13 spectra were obtained by using 2.0 M solutions of compound in $CDCl_3$ solution at 30 °C and were referenced to the central solvent resonance at 76.9 ppm from Me_4Si when recorded. All ^{13}C shifts are reported relative to Me_4Si. Preparative gas–liquid chromatography (GLC) was effected with a Varian A-90-P chromatograph equipped with 0.25-in. aluminum columns. High-resolution mass spectra were obtained on an AEI MS-902 mass spectrometer at 70 eV. Microanalyses were performed by Atlantic Microlab, Inc.

With the exception of the compounds described below, the halides and hydrocarbons used in this work were available from commercial sources and were purified prior to use.

3-Halopentanes (7; X = F, Cl, Br, I). The fluoride was prepared from the tosylate of 3-pentanol by following the literature procedure,[60] and pure 7 (X = F) was obtained in 17.5% yield by careful fractionation of the product mixture (mainly 2-pentene) through a 20-cm vacuum-jacketed column packed with glass helices. The other halides were obtained by the action of the corresponding concentrated aqueous acid on 3-pentanol and distillation of the product after normal workup.

3-Fluoropentane (7, X = F): ^1H NMR (CCl_4) δ 0.96 (t, J = 7.32 Hz, 6 H), 1.56 (complex, 4 H), 4.22 (d, J_{H-F} = 49.1 Hz, 1 H).

3-Chloropentane (7, X = Cl): ^1H NMR (CCl_4) δ 1.03 (t, J = 7.32 Hz, 6 H), 1.70 (complex, 4 H), 3.69 (9 lines, 1 H).

3-Bromopentane (7, X = Br): ^1H NMR (CCl_4) δ 1.04 (t, J = 7.33 Hz, 6 H), 1.82 (complex, 4 H), 3.84 (9 lines, 1 H).

3-Iodopentane (7, X = I): ^1H NMR (CCl_4) δ 1.02 (t, J = 7.32 Hz, 6 H), 1.79 (complex, 4 H), 3.98 (9 lines, 1 H).

3-Halo-3-ethylpentanes (8; X = F, Cl, Br, I). The fluoride was prepared from 3-ethyl-3-pentanol and pyridinium hydrogen fluoride by using the method of Olah.[61] The other halides were obtained by treatment of the alcohol with the corresponding aqueous acid.

3-Fluoro-3-ethylpentane (8, X = F): ^1H NMR (CCl_4) δ 0.87 (t, J = 7.57 Hz, 9 H), 1.57 (dq, J_{H-F} = 25.88, J_{H-H} = 7.57 Hz, 6 H).

3-Chloro-3-ethylpentane (8, X = Cl): ^1H NMR (CCl_4) δ 0.95 (t, J = 7.57 Hz, 9 H), 1.74 (q, J = 7.57 Hz, 6 H).

3-Bromo-3-ethylpentane (8, X = Br): ^1H NMR (CCl_4) δ 0.97 (t, J = 7.32 Hz, 9 H), 1.84 (q, J = 7.32 Hz, 6 H).

3-Iodo-3-ethylpentane (8, X = I): ^1H NMR (CCl_4) δ 0.97 (t, J = 7.30 Hz, 9 H), 1.79 (q, J = 7.30 Hz, 6 H).

***exo*-2-Halonorbornanes (12; X = F, Cl, Br, I).** The fluoride was prepared from norbornene by the method of Olah,[61] and the bromide is commercially available. Literature procedures were followed in the preparation of the chloride[62] and iodide.[63]

7-Halonorbornanes (13; X = Cl, Br, I). The bromide was prepared by the reaction of 7-*tert*-butoxynorbornane with triphenylphosphine and bromine in acetonitrile.[64] The chloride and iodide were obtained by using the same procedure, replacing bromine by chlorine and iodine, respectively.

7-Chloronorbornane (13, X = Cl): mp 39–44 °C (lit.[77] mp 41–44 °C); ^1H NMR ($CDCl_3$) δ 1.30 (t, 4 H), 1.60 (d, 2 H), 1.96 (d, 2 H), 2.20 (m, 2 H), 3.91 (m, 1 H).

7-Bromonorbornane (13, X = Br): bp 96–97 °C (45 mm) [lit.[64] bp 70–72 °C (15–16 mm)]; ^1H NMR ($CDCl_3$) δ 1.30 (m, 4 H), 1.60 (d, 2 H), 1.97 (d, 2 H), 2.25 (m, 2 H), 3.93 (m, 1 H).

7-Iodonorbornane (13, X = I): ^1H NMR ($CDCl_3$) δ 1.30 (m, 4 H), 1.61 (dd, 2 H), 1.95 (dd, 2 H), 2.28 (m, 2 H), 3.82 (m, 1 H). Mass spectroscopic molecular weight calcd for $C_7H_{11}I$ 221.9911, found 221.9904.

7-Fluoronorbornane (13, X = F). A mixture of 10.0 g (68.5 mmol) of silver difluoride in 9.0 mL of dry cyclohexane was cooled to 0 °C under N_2. To this suspension was added 3.2 g (18.3 mmol) of 7-bromonorbornane over a 5-min period. The mixture was heated to gentle reflux to initiate an exothermic reaction. After the originally black AgF_2 became light green, the heat source was removed and the mixture stirred at ambient temperature overnight. Centrifugation of the reaction product effected separation of the liquid from the solid residue. The solid was triturated with 10 mL of pentane followed by centrifugation and removal of the solvent. This procedure was repeated four times, and the combined liquid phases were washed with 10 mL of saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated by careful fractionation through a 20-cm vacuum-jacketed column packed with glass helicies to afford a white semisolid mass. A pure sample of the 7-fluoro compound was isolated in low yield by preparative GLC on a 12-ft, 15% FFAP on Anakrom U (80–100 mesh) column at 110 °C: mp 105–105.5 °C; ^1H NMR ($CDCl_3$) δ 1.21 (t, 2 H), 1.34 (d, 2 H), 1.60 (d, 2 H), 1.90 (d, 2 H), 2.15 (s, 2 H), 4.78 (d, J_{H-F} = 58.10 Hz, 1 H); mass spectroscopic molecular weight calcd for $C_7H_{11}F$ 114.0845, found 114.0844.

2-Chloro-2-cyano-1-methoxybicyclo[2.2.2]oct-5-ene. Following the general procedure of Evans,[65] 106.4 g (1.21 mol) of 2-chloroacrylonitrile was added to 110.1 g (1.0 mol) of 1-methoxycyclohexa-1,4- and -1,3-dienes (from the Birch reduction of anisole) in 200 mL of chloroform containing 600 mg of phenothiazine. The reaction mixture was heated at reflux for 17 h (the 1,4-diene isomerizes to the 1,3 isomer under these conditions),[66] cooled to room temperature, and diluted with 1.0 L of ether. The solution was washed successively with two 50-mL portions of 5% aqueous sodium hydroxide and 50 mL of brine and then dried ($MgSO_4$ plus Na_2SO_4) and concentrated to give a golden oil which was placed under vacuum (0.5 mm) overnight to remove residual solvent and afford 180 g (75%) of product. The oil so obtained was used for the next transformation without further purification. An analytical sample was prepared by crystallization from hexane–ether (5:1) followed by sublimation to give a colorless solid, mp 76–78 °C. Anal. ($C_{10}H_{12}ClNO$) C, H, Cl, N.

1-Methoxybicyclo[2.2.2]oct-5-ene-2-one. By use of the procedure outlined by Evans,[65] 180 g (0.91 mol) of the cyano chloride in 20 mL of ethanol was added to a mixture of 655 g (2.73 mol) of sodium sulfide nonahydrate in ethanol–water (2:1). The reaction mixture was heated to reflux for 8 h, cooled to room temperature and concentrated by rotary evaporation at aspirator pressure to give a viscous red mass containing the salts. The residue was extracted with one 1-L and two 250-mL portions of ether–benzene (3:1). The combined organic phases were washed

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with three 150-mL portions of brine, dried ($MgSO_4$), and concentrated to give a dark oil. Distillation afforded 76.2 g (41% based on the diene) of colorless product: bp 66–70 °C (0.05 mm); IR (neat) 1730, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57–1.92 (m, 4 H), 2.08 (d, J = 2.0 Hz, 2 H), 2.92 (m, 1 H), 3.48 (s, 3 H), 6.20 (d, J = 8.4 Hz, 1 H), 6.42 (apparent t, J = 6.4 Hz, 1 H); mass spectroscopic molecular weight calcd for $C_9H_{12}O_2$ 152.0837, found 152.0836.

1-Methoxybicyclo[2.2.2]octan-2-one. Hydrogenation of 65.0 g (0.43 mol) of 1-methoxybicyclo[2.2.2]oct-5-ene-2-one in 200 mL of dry ethyl acetate over 2.0 g of 10% palladium-on-carbon at 60 psi of H_2 for 8 h afforded the product quantitatively: ^1H NMR ($CDCl_3$) δ 1.64–1.92 (br m, 8 H), 2.05 (m, 1 H), 2.27 (d, J = 2.90 Hz, 2 H), 3.27 (s, 3 H). Anal. ($C_9H_{14}O_2$) C, H.

1-Methoxybicyclo[2.2.2]octane (14, X = OCH_3). To a solution of 22.3 g (0.35 mol) of potassium hydroxide and 16.0 g (0.26 mol) of 85% hydrazine hydrate in 300 mL of ethylene glycol was added 15.4 g (0.10 mol) of 1-methoxybicyclo[2.2.2]octan-2-one. The mixture was warmed to 195 °C over 1 h and refluxed gently for an additional hour. The flask was then fitted for distillation, and approximately 25 mL (two layers) of liquid was collected over a period of 1 h at 195 °C. Subsequent dropwise addition of 250 mL of water to the reaction mixture over a period of 3 h afforded a second fraction of distillate (approximately 200 mL). The combined distillates were extracted with three 80-mL portions of pentane–ether (1:1), the organic phase was dried ($MgSO_4$), and the volatiles were removed by distillation through a 20-cm vacuum-jacketed column packed with glass helicies. The residue was distilled to give 7.3 g (52%) of product, bp 184–186 °C (lit.[67] bp 185–190 °C).

1-Halobicyclo[2.2.2]octanes (14; X = F, Cl, Br, I). The compounds were prepared by the reaction of 1-methoxybicyclo[2.2.2]octane with the corresponding acetyl halide.[67]

1-Fluorobicyclo[2.2.2]octane (14, X = F): mp (sealed tube) 172–174 °C (lit.[69] mp ca. 152 °C); ^1H NMR (CCl_4) δ 1.51 (m, 1 H), 1.71 (m, 12 H).

1-Chlorobicyclo[2.2.2]octane (14, X = Cl): mp 104.5–105 °C (lit.[67] mp 103.5–104.6 °C); ^1H NMR (CCl_4) δ 1.57 (6 lines, 1 H), 1.72 (m, 6 H), 1.95 (m, 6 H).

1-Bromobicyclo[2.2.2]octane (14, X = Br): mp 66–66.5 °C (lit.[67] mp 63.5–64.5 °C); ^1H NMR (CCl_4) δ 1.60 (6 lines, 1 H), 1.75 (m, 6 H), 2.17 (m, 6 H).

1-Iodobicyclo[2.2.2]octane (14, X = I): mp 27–28 °C (lit.[67] mp 27.5–28.5 °C); ^1H NMR (CCl_4) δ 1.67 (m, 1 H), 1.74 (m, 6 H), 2.42 (m, 6 H).

7,7-Dimethylnorbornane (18, X = H). Hydrogenation of 2.8 g (22.9 mmol) of apobornene[68] in methanol–olefin-free pentane (7:1) over 400 mg of 10% palladium-on-carbon at 50 psi of H_2 for 18 h gave a virtually quantitative yield of product from which samples of 18 (X = H) were most conveniently isolated by preparative GLC on a 12-ft, 15% FFAP on Anakrom ABS (80–100 mesh) column at 85 °C: mp 78–80 (lit.[69] mp 88–89 °C); ^1H NMR ($CDCl_3$) δ 0.95 (s, CH_3, 6 H), 1.16 (d, *endo*-H, J = 7.35 Hz, 4 H), 1.50 (m, bridgehead, 2 H), 1.78 (d broadened by unresolved coupling, *exo*-H, J = 7.35 Hz, 4 H).

***exo*-2-Chloro-7,7-dimethylnorbornane (18, X = Cl).** By use of the procedure of Brown,[70] hydrogen chloride was added[71] to a solution of apobornene[68] in dichloromethane. Pure samples of product were obtained by preparative GLC on a 12-ft, 15% FFAP on Anakrom ABS (80–100 mesh) column at 140 °C: mp 52–53 °C (lit.[70] mp 55–56 °C); ^1H NMR ($CDCl_3$) δ 0.97 (s, *anti*-CH_3, 3 H), 1.05 (m, 2 H), 1.28 (s, *syn*-CH_3, 3 H), 1.65–1.90 (complex, 5 H), 2.18 (complex, bridgehead, 1 H), 3.90 (dd, C(2) H, J = 4.4, 8.5 Hz, 1 H). The chemical shifts of the CH_3 groups and the H on C(2) are consistent with those previously reported.[72] It is to be noted that this compound rearranges rapidly upon attempted column chromatography using neutral, basic, or acidic alumina.

***exo*-2-Bromo-7,7-dimethylnorbornane (18, X = Br).** By use of an apparatus similar to that described by Brown,[71] hydrogen bromide (generated by dehydration of aqueous HBr with sulfuric acid and removal of the bromine produced by passage of the gas through a series of cold traps held at −55 °C) was added to apobornene[68] (800 mg, 6.5 mmol) in 10 mL of dichloromethane. After the uptake of 1 equiv of hydrogen bromide, the reaction mixture was cooled to −78 °C, and residual HBr was removed under high vacuum. The cold product was poured into 50 mL of dry pentane containing 4.0 g of anhydrous potassium carbonate, stirred vigorously for 1.5 h, filtered, and concentrated at reduced pressure to give 1.3 g of colorless oil. The product was unstable to both column chromatography and GLC. The ^1H NMR spectrum showed that the product was composed of 93% *exo*-2-bromo-7,7-dimethylnorbornane and 7% of the *endo*-2-bromo isomer: ^1H NMR ($CDCl_3$) δ 0.96 (s, *anti*-CH_3, 3 H), 1.12 (m, 2 H), 1.32 (s, *syn*-CH_3, 3 H), 1.60–2.10 (m, 5 H), 2.37 (complex, bridgehead, 1 H), 3.95 (dd, C(2) H, J = 4.7, 8.5 Hz, 1 H); mass spectroscopic molecular weight calcd for $C_9H_{15}Br$ 202.0358, found 202.0362.

***exo*-2-Iodo-7,7-dimethylnorbornane (18, X = I).** By use of an apparatus similar to that described by Brown,[71] hydrogen iodide (generated by dehydration of aqueous HI with phosphorus pentoxide and removal of the iodine produced by passage of the gas through a cold trap filled with glass wool at −30 °C) was added to 1.0 g (8.2 mmol) of apobornene[70] in 15 mL of dichloromethane. After 1 equiv of HI had been taken up, the reaction product was worked up as described above for the bromide. NMR analysis revealed that the product (a colorless liquid) contained 91% *exo*-2-iodo-7,7-dimethylnorbornane and 9% of the *endo*-2-iodo isomer: ^1H NMR ($CDCl_3$) δ 0.98 (s, *anti*-CH_3, 3 H), 1.08 (m, 2 H), 1.41 (s, *syn*-CH_3, 3 H), 1.55–2.00 (m, 5 H), 2.26 (complex, bridgehead, 1 H), 3.99 (dd, C(2) H, J = 5.14, 8.82 Hz, 1 H); mass spectroscopic molecular weight calcd for $C_9H_{15}I$ 250.0224, found 250.0205.

Spectral Assignments. For the most part, ^{13}C chemical shifts were made on the basis of one or more of the following techniques: chemical shift substituent effects,[7-19] multiplicities in the completely coupled spectrum, line intensities in gated-proton-decoupled spectra, off-resonance-decoupled multiplicities, and selective proton-decoupling experiments. With the exception of 2-methylpropane (6, Table II), the hydrocarbon assignments agree with those in the literature.[7-19] The assignment of chemical shift in 2-methylpropane [$\delta_{C(1)}$ 24.61, $\delta_{C(2)}$ 23.30] is the reverse of that previously reported[13] and is based on both off-resonance decoupling and comparison with the shifts observed for 2-methylpropane-2-*d* (provided by Professor M. Saunders, Yale University).

The chemical shifts of the simple alkyl halides (1–6, Table I) are consistent with previous reports,[7-19,31] and the 3-pentyl (7) and 3-ethyl-3-pentyl halides (8) were unambiguously assigned by selective proton decoupling. Analysis of the ^{13}C spectra of the cyclobutyl halides (9) has been presented,[1] and the cyclopentyl halides (10) were assigned in a similar fashion. The cyclohexyl halide (12) chemical shifts are consistent with those reported by Sergeyev[73] and Lippmas.[74] The 1-halobicyclo[2.2.2]octane (14) assignments are in accord with those previously reported.[75] The chemical shifts of the following sets of halides, as noted in Table I, were taken from the literature: **15**,[43] **16**,[44] and **17**.[44]

The ^{13}C nuclei of *exo*-2-fluoronorbornane (12, X = F) were assigned by consideration of the magnitude of $J_{^{13}C-F}$ for each nucleus (in addition to the techniques noted above), and the chemical shifts are in agreement with those reported for this compound.[76] The assignments for *exo*-2-chloro- (12, X = Cl) and *exo*-2-bromonorbornane (12, X = Br) presented in Table I are consistent with those reported by Wilson and Stothers.[10] The *exo*-2-iodonorbornane (12, X = I) analysis was done by analogy with the other halides.

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The syn and anti carbon nuclei in 7-chloronorbornane (**13**, X = Cl) were unambiguously distinguished by recording of the ^{13}C spectrum of *exo,exo*-2,3-dideuterio-*syn*-7-chloronorbornane (prepared as described).[77] Long-range $^3J_{^{13}C-F}$ coupling constants were employed in the analysis of 7-fluornorbornane (**13**, X = F) to distinguish the syn and anti positions: δ 26.52 (syn), $^3J_{^{13}C-F}$ = 1.72 Hz; δ 25.18 (anti), $^3J_{^{13}C-F}$ = 8.60 Hz. The largest coupling was assigned to the γ-*anti*-carbon in accord with the analysis of such coupling given by Schneider.[78] The syn and anti carbon nuclei in 7-iodonorbornane (**13**, X = I) were correlated with the assigned protons in the molecule by selective proton decoupling experiments (*exo-syn*-^{1}H, δ 1.95; *exo-anti*-^{1}H, δ 1.62; *endo-syn*- and *endo-anti*-^{1}H, δ 1.30; for **13**, X = I) to give the results in Table I for this compound. The *syn*- and *anti*-carbons in 7-bromonorbornane (**13**, X = Br) differ by only 0.07 ppm (i.e., δ 27.33 and 27.26), and it was not possible to unambiguously assign these resonances.

The *exo*-2-halo-7,7-dimethylnorbornanes (**18**, X = Cl, Br, I) were prepared in an attempt to probe the effect of proximate δ groups. While it proved possible to assign the chemical shifts of C(1), C(2), C(3), C(4), and C(7) in these molecules by a combination of the techniques outlined above, it was not possible to unambiguously distinguish C(5) from C(6), and the assignments of these resonances in Table I were made by analogy. The *syn*- and *anti*-7-methyl groups in all of the *exo*-2-halo-7,7-dimethyl compounds differed only slightly in chemical shift, and no effort was made to distinguish between the methyl nuclei since these data were not used in the factor analysis.

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Registry No. **1** (X = F), 593-53-3; **1** (X = Cl), 74-87-3; **1** (X = Br), 74-83-9; **1** (X = I), 74-88-4; **2** (X = F), 353-36-6; **2** (X = Cl), 75-00-3; **2** (X = Br), 74-96-4; **2** (X = I), 75-03-6; **3** (X = F), 460-13-9; **3** (X = Cl), 540-54-5; **3** (X = Br), 106-94-5; **3** (X = I), 107-08-4; **4** (X = F), 420-26-8; **4** (X = Cl), 75-29-6; **4** (X = Br), 75-26-3; **4** (X = I), 75-30-9; **5** (X = F), 2366-52-1; **5** (X = Cl), 109-69-3; **5** (X = Br), 109-65-9; **5** (X = I), 542-69-8; **6** (X = F), 353-61-7; **6** (X = Cl), 507-20-0; **6** (X = Br), 507-19-7; **6** (X = I), 558-17-8; **7** (X = F), 41909-29-9; **7** (X = Cl), 616-20-6; **7** (X = Br), 1809-10-5; **7** (X = I), 1809-05-8; **8** (X = F), 649-80-9; **8** (X = Cl), 994-25-2; **8** (X = Br), 73908-04-0; **8** (X = I), 75066-51-2); **9** (X = F), 666-16-0; **9** (X = Cl), 1120-57-6; **9** (X = Br), 4399-47-7; **9** (X = I), 38557-29-8; **10** (X = F), 1481-36-3; **10** (X = Cl), 930-28-9; **10** (X = Br), 137-43-9; **10** (X = I), 1556-18-9; **11** (X = F), 372-46-3; **11** (X = Cl), 542-18-7; **11** (X = Br), 108-85-0; **11** (X = I), 626-62-0; **12** (X = F), 765-92-4; **12** (X = Cl), 765-91-3; **12** (X = Br), 2534-77-2; **12** (X = I), 30983-85-8; **13** (X = F), 70279-04-8; **13** (X = Cl), 765-80-0; **13** (X = Br), 13237-88-2; **13** (X = I), 70279-05-9; **14** (X = F), 20277-22-9; **14** (X = Cl), 2064-03-1; **14** (X = Br), 7697-09-8; **14** (X = I), 931-98-6; **15** (X = F), 63160-84-9; **15** (X = Cl), 15158-55-1; **15** (X = Br), 15292-76-9; **15** (X = I), 63160-85-0; **16** (X = F), 768-92-3; **16** (X = Cl), 935-56-8; **16** (X = Br), 768-90-1; **16** (X = I), 768-93-4; **17** (X = F), 16668-83-0; **17** (X = Cl), 7346-41-0; **17** (X = Br), 7314-85-4; **17** (X = I), 18971-91-0; **18** (X = F), 70279-06-0; **18** (X = Cl), 22768-98-5; **18** (X = Br), 70279-07-1; **18** (X = I), 70279-08-2; 2-chloroacrylonitrile, 920-37-6; 1-methoxycyclohexa-1,4-diene, 2886-59-1; 1-methoxycyclohexa-1,3-diene, 2161-90-2; 1-methoxybicyclo[2.2.2]oct-5-en-2-one, 38213-08-0; apoborene, 6541-60-2.

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Coenzyme Models. 26. Facile Oxidation of Aldehydes and α-Keto Acids by Flavin as Catalyzed by Thiazolium Ion and Cationic Micelle[1]

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The reaction sequence of acyloin condensation of aldehydes which is catalyzed by *N*-hexadecylthiazolium bromide (HxdT) in the CTAB micelle was readily diverted by added 3-methyltetra-*O*-acetylriboflavin (MeFl) to the oxidation reaction to afford carboxylic acids. Similarly, the micellized thiazolium ion plus MeFl system efficiently catalyzed the decarboxylative oxidation of aliphatic α-keto acids but scarcely catalyzed that of aromatic α-keto acids. In contrast, hydrophilic thiazolium ions such as *N*-benzylthiazolium bromide (BzlT), thiamine, and thiamine pyrophosphate (TPP) were less effective catalysts. The reactions were zero-order in MeFl and first-order in HxdT and substrates, the apparent second-order rate constants being enhanced by factors of 10^2–10^4 in comparison to those in the nonmicellar system. On the basis of the kinetic examination and the product analysis, we proposed that the reactions involve oxidative trapping by MeFl of the intermediate formed by the rate-limiting deprotonation or decarboxylation from the HxdT–substrate adducts. This means that the intermediate of the thiazolium ion catalysis (active aldehyde) serves as substrate for the flavin oxidation. This is the first nonenzymatic example for the synergistic catalysis of flavin coenzyme and TPP coenzyme. The relevance of the reactions to biological systems (in particular, to pyruvate dehydrogenase which requires FAD and TPP as cofactors) is discussed. Since the 2-acyl group of the oxidation products (2-acylthiazolium ions) is sensitive to nucleophiles, the reaction is readily applicable to synthesis of esters from aldehydes.

Recently, it was proposed that some flavin-dependent enzymes employ carbanion intermediates during the course of the oxidation of bound substrates.[2,3] In a previous publication of this series,[4] we demonstrated that the application of the concept "flavin oxidation of carbanion" to organic chemistry is very useful in exploring a new class of oxidation reactions. A successful example is seen in the

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