Deuterium Chemical Shifts and Chemical Shift Parameters in Methylcyclohexanes

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Natural-abundance, proton-decoupled deuterium NMR spectra were used in conjunction with proton spectra to simplify the hydrogen chemical shift assignments in 17 methylcyclohexanes. The simple deuterium spectra were interpreted by use of symmetry, hydrogen-scalar coupling information, and linear parameters obtained with a multiple regression analysis. The nonnegligible parameters primarily were those with either structural or spatial proximity between the ring hydrogen and methyl substituent. Three compounds which appear to have substantial nonchair contributions to their conformational equilibria are identified and discussed. The possible origin of four highly unique, vicinal methyl-hydrogen parameters is suggested.

Introduction

Deuterium has long been used in nuclear magnetic resonance studies as a kinetic, mechanistic, and structural probe.[1-6] Although the feasibility of ^2H NMR studies at natural abundance was recognized as a consequence of the development of Fourier transform methods and high-field spectrometers, most work involves enrichment as a result of the ready availability and relative ease of isotopic incorporation.

Although the development of ^1H NMR preceded that of proton-decoupled ^{13}C NMR, the single peak characteristics of the latter method produced a readily used structural and conformational probe. Proton spectra in many complex molecules suffer from banding and large second-order effects which make interpretation difficult if not impossible and can reduce the value of ^1H spectra in structural analysis. Thus ^{13}C came to be almost exclusively used in some conformational problems with only minor consideration given to supporting ^1H data.

As with other rare nuclei, such as ^{13}C, proton-decoupled, natural-abundance ^2H spectra exhibit single resonances for each chemically distinct site. Although ^2H has a lower sensitivity at natural abundance than either ^{13}C or ^{15}N, the difficulty of detection is not so great as to preclude successful work. In comparison to ^1H, ^{13}C is more difficult to detect by a factor of 1.7×10^{-4}, ^{15}N by a factor of 3.7×10^{-6}, and ^2H by a factor of 1.5×10^{-6}.[7] Deuterium relaxation is dominated by the quadrupolar mechanism with short T_1 values assisting in the accumulation of data. NOE contributions to line intensities are negligible due to the unimportance of the dipolar relaxation process. Very high-field instruments, however, are necessary for sufficient resolution to separate closely placed resonances resulting from the low magnetogyric ratio of ^2H [$\gamma(^2H)/\gamma(^1H) = 0.1535$].

Chemical shifts of ^2H in ppm are essentially identical with the corresponding ^1H shifts, although small discrepancies have been noted.[8-10] The patterns of chemical shifts, nonetheless, are the same for the two isotopes, and work with rigorous temperature and solvent control was not required to explore the conformational features important in ^1H and ^2H shifts. The single resonances and structurally dependent chemical shifts of ^2H natural-abundance spectra provide a powerful tool for unscrambling the numerous overlapping multiplets in many ^1H spectra.

In this study the chemical shifts of 17 methylcyclohexanes have been acquired using a combination of techniques: natural-abundance ^2H spectra, ^1H spectra, ^1H-^1H multiplets, and selective decoupling. These data have been treated with multivariate statistical methods (stepwise multiple linear regression) to correlate structural features important in hydrogen chemical shieldings.

Experimental Section

The methylcyclohexanes were obtained from either standard sources or the American Petroleum Institute. All were in excess of 99% purity. These compounds can be grouped into three classes;[11] those with two chair conformations of equal energy which rapidly interconvert at room temperature, those with a single energetically favored chair conformation, and those with two conformations of intermediate energy differences leading to a substantial contribution from less favored forms (Table I).

The deuterium spectra were aquired on neat compounds with 10% Me_4Si added for reference in 10-mm OD tubes. The spectra were run unlocked on a Bruker WM-500 located at the Southern California Regional NMR Facility at the California Institute of Technology. Shimming was performed on protons. From 100 to 400 transients were accumulated with a modest amount of sensitivity enhancement to supress random noise. In every case, however, the line widths were less than 0.7 Hz. The proton spectra were obtained on samples in 50% $CDCl_3$ for shimming and lock and 10% Me_4Si for reference on a Varian SC-300 in 5-mm OD tubes. Ten to twenty transients were accumulated and transformed. A comparison of representative proton and deuterium spectra is provided in Figure 1 for methylcyclohexane.

Results and Discussion

A. Spectral Assignments. i. Methyl Deuterium Shifts. The methyl peak assignments given in Table II were made on the basis of symmetry considerations, selective decoupling of protons, and comparison with compounds previously assigned unambiguously. The methyl shifts in Table II are designated by the compound's name and item numbers given in parentheses. When only one methyl peak appears in a compound, the methyl assignments are unequivocal (items 11, 15, 21, 27, 31, 45, 49, and 124). Since only one methyl peak appears in 1,1,4-trimethylcyclohexane (77), accidental degeneracy is assumed. For 1-*Cis*-3,*trans*-5-trimethylcyclohexane (131, 132) two peaks of unequal intensity are observed and symmetry

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(10) Jensen, H.; Schaumburg, K. *Mol. Phys.* **1971**, *22*, 1041.
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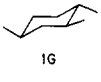
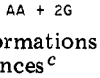
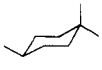
Table I

position of Me			ΔE, kcal/mol
a. Methylcyclohexanes with Equal Energy Conformations[a]			
1,1			0
	2G	2G	
1,*cis*-2			0
	2G	2G	
1,*trans*-3			0
	2G	2G	
1,*cis*-4			0
	2G	2G	
b. Methylcyclohexanes with Preferred Conformation[b]			
1,*trans*-2			~2.7
	1G	4G	
1,*cis*-3-			~5.5
		AA + 2G	
1,*trans*-4-			~3.6
		4G	
1,1,3-			~3.7
	2G	AA + 2G	
1,*trans*-2,*cis*-3-			~5.5
	2G	AA + 4G	
1,*trans*-2,*trans*-4-			~6.4
	1G	AA + 4G	
1,*cis*-3,*cis*-5-			~11.1
		3AA	
1,*cis*-3,*trans*-5-			~3.7
	2G	AA + 2G	
c. Methylcyclohexanes with Conformations of Intermediate Energy Differences[c]			
monosubstituted			~1.8
		2G	
1,1,2			~0.9
	3G	4G	
1,1,4			~1.8
	2G	4G	
1,*cis*-2,*trans*-3-			~0.9
	3G	4G	
1,*trans*-2,*cis*-4-			~0.9
	3G	4G	

[a] G ~ 0.9 kcal/mol. [b] G ~ 0.9 kcal/mol; AA ~ 2.7 kcal/mol. [c] G ~ 0.9 kcal/mol.

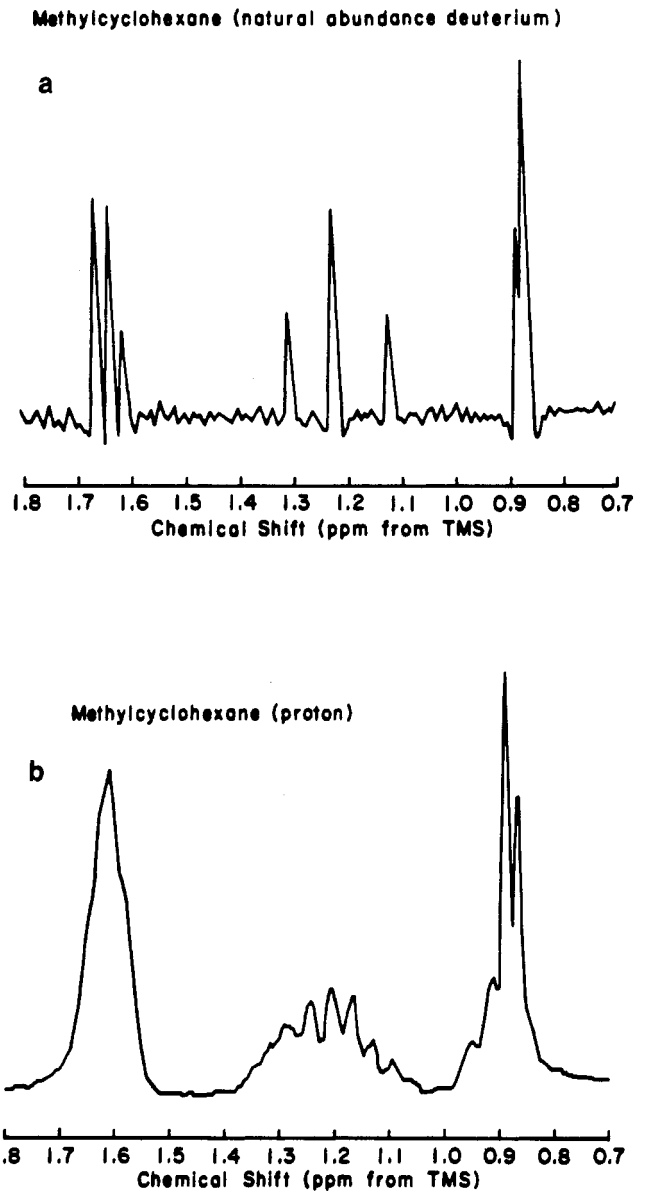


Figure 1. Natural-abundance, proton-decoupled deuterium and proton spectra of methylcyclohexane showing the clearly resolved single peaks in the deuterium spectrum in contrast to the overlapping multiplets in the proton spectrum. Spectra were digitized and replotted to the same scale.

considerations dictate the assignment of the 5-axial methyl downfield of the degenerate 1,3-equatorial methyl peak. Likewise, the peak intensities determine the assignments of the methyl peaks in 1,*cis*-2,*trans*-3-trimethylcyclohexane (95, 96) with the 1-axial methyl assigned upfield of the two equatorial methyls. Although three peaks are expected in 1,*trans*-2,*cis*-4-trimethylcyclohexane (106–108) only two were observed, which indicates accidental degeneracy in the compound. The 1-equatorial and 2-equatorial methyls are structurally very similar to the 1- and 2-equatorial sites in 1,*trans*-2-dimethylcyclohexane. This similarity can be attributed to the lack of interaction with the spatially and structurally remote 4-equatorial methyl. In 1,*trans*-2,*cis*-3-trimethylcyclohexane (84, 85) the methyls again were assigned unequivocally on the basis of peak intensities. The methyls in 1,1,2-trimethylcyclohexane (58–60) were assigned by reference to methyl shifts in compounds with similar structural features.

ii. Ring Deuterium Assignments. The assignments of hydrogens (and deuterons) attached to ring carbons were made by using the combination of techniques listed above.

Table II. Chemical Shifts for the Methylcyclohexanes

cyclohexane	item	proton[a]	δ (Me_4Si)	proton values[b]	cyclohexane	item	proton[a]	δ (Me_4Si)	proton values[b]
unsubstituted	1	1–6 a,e	1.40	1.44	1,1,3-trimethyl	61	2 a	0.71*	(1.40)
	2	1–6 a	--	1.17[c]		62	4a	0.75*	(1.40)
	3	1–6 e	--	1.65[c]		63	6a	1.03	(1.40)
methyl	4	2, 6 a	0.87	(1.43)		64	6 e	1.33	(1.40)
	5	4 a	1.12	(1.43)		65	2 e	1.33	(1.40)
	6	3, 5 a	1.22	(1.43)		66	5 a	1.42	(1.40)
	7	1 a	1.30	1.48		67	5 e	1.50	(1.40)
	8	4 e	1.61	(1.43)		68	3 a	1.50	(1.40)
	9	3, 5 e	1.64*	(1.43)		69	4 e	1.64	(1.40)
	10	2, 6 e	1.66*	(1.43)		70	methyl 1a,e	0.80	0.88
	11	methyl	0.86	0.89		71	methyl 3e	0.83	0.83
1,1-dimethyl	12	2, 6	1.22	(1.30)	1,1,4-trimethyl[c]	72	3, 5 a	1.08	
	13	4	1.35	(1.39)		73	2, 6 a	1.17	
	14	3, 5	1.43	(1.39)		74	4 a	1.23	
	15	methyl	0.88	0.88		75	2, 6 e	1.34	
1,*cis*-2-dimethyl[d]	16	3e, 6a	1.28	(1.42)		76	3, 5 e	1.46	
	17	4e, 5a	1.34	(1.42)		77	methyl	0.88[g]	
	18	4a, 5e	1.39	(1.42)	1,*trans*-2,*cis*-3-trimethyl	78	2 a	0.59	0.77
	19	3a, 6e	1.51	(1.42)		79	4, 6 a	0.97*	(1.35)
	20	1, 2	1.64	1.65		80	1, 3 a	1.00*	1.17
	21	methyl	0.83	0.86		81	5 a	1.28	(1.35)
1,*trans*-3-dimethyl[d]	22	4e, 6a	1.12	(1.40)		82	4, 6 e	1.61	(1.35)
	23	2	1.28	(1.40)		83	5 e	1.63	(1.35)
	24	5	1.45	(1.40)		84	methyl 1, 3e	0.92	0.92
	25	4a, 6e	1.51	(1.40)		85	methyl 2e	0.90	0.90
	26	1, 3	1.75	1.75	1,*cis*-2,*trans*-3-trimethyl[e]	86	4 a	0.86	
	27	methyl	0.90	0.90		87	3 a[h]	1.11	
1,*cis*-4-dimethyl[d]	28	2, 6a, 3, 5e	1.23	(1.42)		88	2 a[h]	1.20	
	29	2, 6e, 3, 5a	1.48	(1.42)		89	5 a[h]	1.32	
	30	1, 4	1.59	1.49		90	6 e[h]	1.32	
	31	methyl	0.91	0.92		91	6 a[h]	1.32	
1,*trans*-2-dimethyl	32	1, 2 a	0.92	1.02		92	5 e[h]	1.46	
	33	3, 6 a	0.93	(1.34)		93	4 e[h]	1.48	
	34	4, 5 a	1.21	(1.34)		94	1 e	1.65	
	35	4, 5 e	1.61*	(1.34)		95	methyl 1a	0.75	
	36	3, 6 e	1.65*	(1.34)		96	methyl 2,3e	0.81	
	37	methyl	0.88	0.89	1,*trans*-2,*trans*-4-trimethyl	97	3 a	0.64	(1.27)
1,*cis*-3-dimethyl	38	2a	0.62	0.52		98	5 a	0.86*	(1.27)
	39	4, 6 a	0.85	(1.40)		99	1 a	0.87*	0.90
	40	5 a	1.32	(1.40)		100	2 a	0.97*	0.90
	41	1, 3 a	1.40	1.18		101	6 a	0.98*	(1.27)
	42	5e	1.70	(1.40)		102	4 a	1.35	1.15
	43	4, 6 e	1.70	(1.40)		103	5 e	1.59	(1.27)
	44	2e	1.75	1.58		104	6 e	1.62	(1.27)
	45	methyl	0.94	0.84		105	3 e	1.63	(1.27)
1,*trans*-4-dimethyl	46	2, 3, 5, 6 a	0.90	(1.35)		106	methyl 1e	0.88	0.90
	47	1, 4 a	1.24	1.25		107	methyl 2e	0.88	0.90
	48	2, 3, 5, 6 e	1.65	(1.35)		108	methyl 4e	0.86	0.90
	49	methyl	0.86	0.90	1,*trans*-2,*cis*-4-trimethyl[e]	109	1 a	1.00	1.13
1,1,2-trimethyl[e]	50	3, 6 a	1.11	(1.32)		110	6 a	1.20	1.55
	51	4 a[h]	1.18	(1.32)		111	3 a	1.20	(1.39)
	52	2 a[h]	1.20	(1.32)		112	2 a	1.26	(1.39)
	53	6 e[h]	1.35	(1.32)		113	5 e[h]	1.37	(1.39)
	54	5 a[h]	1.37	(1.32)		114	3 e[h]	1.39	(1.39)
	55	5 e[h]	1.39	(1.32)		115	5 a[h]	1.43	(1.39)
	56	4 e	1.45	(1.32)		116	6 e	1.48	(1.39)
	57	3 e	1.63	(1.32)		117	4 e	1.85	1.88
	58	methyl 1a	0.80	(0.83)		118	methyl 1e	0.88	(0.89)
	59	methyl 1e	0.88	(0.83)		119	methyl 2e	0.91	(0.89)
	60	methyl 2e	0.76	(0.83)		120	methyl 4a	0.94	0.97
					1,*cis*-3,*cis*-5-trimethyl	121	2, 4, 6 a	0.47	(1.06) 0.47[f]
						122	1, 3, 5 a	1.40	1.40,1.40[f]
						123	2, 4, 6 e	1.65	(1.06) 1.64[f]
						124	methyl	0.77	0.88, 0.86[f]
					1,*cis*-3,*trans*-5-trimethyl	125	2 a	0.49	(0.98) 0.47[f]
						126	4, 6 a	1.02	(1.28) 1.01[f]
						127	4, 6 e	1.42	(1.28) 1.52 ± 0.10[f]
						128	1, 3 a	1.57	1.56,1.52 ± 0.10[f]
						129	2 e	1.60	(0.98) 1.52 ± 0.10[f]
						130	5 e	1.96	2.00,2.00[f]
						131	methyl 1,3 e	0.82	0.83,0.83[f]
						132	methyl 5a	0.96	0.97,0.97[f]

[a] Indicates carbon to which proton is attached and spatial orientation. [b] All literature values are from ref 11 unless otherwise noted. Values in parentheses indicate the center of nonresolvable proton bands. [c] Anet, F. A. L.; Ahman, M.; Hall, L. D. *Proc. Chem. Soc., London* **1964**, also Bovey, F. A., Hood, F. P.; Anderson, E. W.; Kornegay, R. L.; *Ibid.* **1964**, *146*. [d] For compounds with signal averaged spectra, the a, e designations refer to the conformation with the 1e methyl. [e] Assignments for these compounds are based on a linear combination of conformations (see Discussion). [f] Segre, A.; Musher, J. I. *J. Am. Chem. Soc.*, **1967**, *89*, 706. [g] Methyl shifts were not resolved in this compound indicting accidental degeneracy. [h] Assignment tentative within groups of closely spaced resonanes. * Indicates shifts close in magnitude and final assignment made on the basis of ordering during the regression analysis.

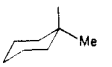
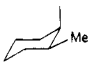
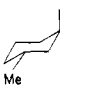
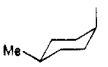
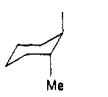
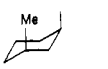
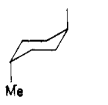
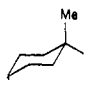
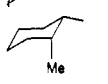
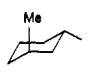
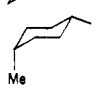
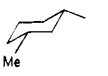
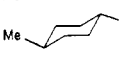
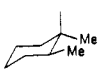
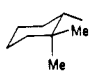
The paucity of accurate data for proton shifts taken from the literature and listed in Table II emphasizes the value of natural-abundance ^2H NMR in interpreting spectra of this general type. In this relatively simple class of compounds substantial banding occurs. The 1,*cis*-3-dimethyl- (38–44), 1,*trans*-4-dimethyl- (46–48), 1,1-dimethyl- (12–14), 1,*cis*-3,*cis*-5-trimethyl- (121–123), and 1,*cis*-3,*trans*-5-trimethylcyclohexane (125–130) shifts were assigned unequivocally on the basis of line intensities in the deuterium spectra and coupling patterns in the proton spectra. In 1-methyl- (4–10), 1,*trans*-2-dimethyl- (32–36), 1,1,3-trimethyl- (61–69), and 1,*trans*-2,*trans*-4-trimethylcyclohexane (97–105), tentative assignments were made by using some of the above methods where possible, with final assignments for some close and ambiguous shifts made on the basis of ordering in the regression analysis. The values for the axial and equatorial shifts in cyclohexane may be obtained (footnote *c* in Table II) at low temperatures where the chair–chair interconversion is slowed sufficiently to remove the effect of averaging.

B. Regression Analysis of Data. The set of parameters obtained in a preliminary stepwise multiple regression analysis using the STAT80 statistics package implemented on a DEC-20 system are given in Table III. Parameter designations indicate axial (A) or equatorial (E) ring hydrogen and the relative position of substituted methyls (1 is a geminal carbon while 4 labels the methyl attached to the 4 carbon cross ring from the designated deuterium, a is an axial methyl, and e is an equatorial methyl). Two distortional parameters were required to account for nonlinearity of multiple substitutions at geminal or vicinal sites. The table includes these two distortional factors and the complete set of primary structural relationships which were found to be of greatest significance. Ring distortions due to multiple methyl substitutions are expected to affect only the local chemical shifts to any great degree since ring flattening due to an axial methyl only occurs locally.[12,13] Distortions due to sterically perturbed vicinal diequatorial methyls are of relatively low energy (one gauche interaction) and affect only the axial hydrogens attached directly to the adjacent ring carbons with vicinal methyls.

A regression analysis using the above set of 16 parameters resulted in a multiple correlation coefficient of 0.9959 and a standard error of the estimate of 0.0348 ppm. This regression indicated that it was possible to eliminate five of the primary structural parameters, A(4a), E(4a), E(2e), E(3e), and E(4e), as statistically insignificant at the 0.05 confidence level. A final regression was then performed using the remaining 11 structural and distortion parameters. The values for these parameters appear in Table III along with the statistical information. The success of this fit is indicated by the statistical data and the plot of the 78 observed vs. predicted shift values given in Figure 2. The plot confirms that linear parameters are suitable for compounds used in this regression.

The existence of some residuals larger than the experimental error in the regression indicates that other subtle structural features may be important. Even so, the selected parameter set is felt to be sufficiently inclusive for most identification purposes. In general the proximate methyl substituent groups dominate the hydrogen shieldings. Two factors appear to be important: (1) the number of bonds separating the ring hydrogen from the interacting methyl, and (2) proximate cis or trans rela-

Table III. Structural Parameter Set for Use in Regression Analysis

parameter	primary structural features	no. of occurrences	value
	Axial Parameters		
A(no methyls)		1	−0.480 ± 0.0074
A(1e) (trans)		16	0.127 ± 0.0061
A(2e) (cis)		33	−0.309 ± 0.0040
A(3e) (trans)		30	0.074 ± 0.0034
A(4e) (cis)		17	−0.043 ± 0.0047
A(2a) (trans)		10	0.214 ± 0.0064
A(3a) (cis)		10	0.157 ± 0.0064
A(4a) (trans)		7	negligible
	Equatorial Parameters		
E(no methyls) (intercept)		1	1.642 ± 0.0127
E(1a) (trans)		4	0.296 ± 0.0104
E(2a) (cis)		9	−0.197 ± 0.0098
E(3a) (trans)		7	−0.154 ± 0.0078
E(4a) (cis)		5	negligible
E(2e) (trans)		27	negligible
E(3e) (cis)		26	negligible
E(4e) (trans)		14	negligible
	Distortional Features		
A(1e,2e)		6	−0.054 ± 0.0067
E(2a,2e)		4	−0.109 ± 0.0118

Parameters are named for structural relationships. The initial letter (A or E) indicates axial or equatorial ring hydrogen. The number indicates the ring carbon relative to the hydrogen site (1 is geminal) to which the methyl is attached. The following letter (a or e) indicates whether the methyl is axial or equatorial. For multiple substitutions in the distortion parameters, each methyl is designated. Multiple correlation coefficient = 0.9947. Standard error of estimate = 0.0378.

(12) Geise, H. J.; Mulhoff, F. C.; Altona, C. *J. Mol. Struct.* **1972**, *13*, 211.
(13) Altona, C.; Sundaralingam, M. *Tetrahedron* **1970**, *26*, 925.

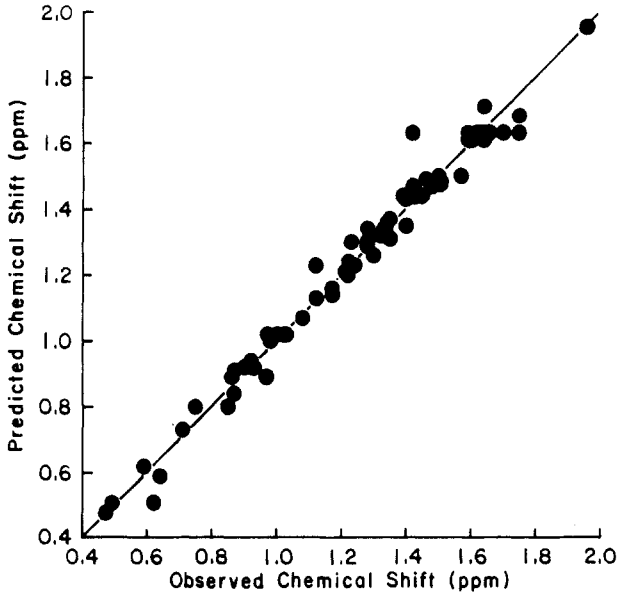


Figure 2. Predicted chemical shifts for the 12 compounds used in the regression analysis are plotted vs. the observed values. The linear regression model fits the shifts for these compounds well, indicating that these 12 compounds exist primarily in chair conformations. The standard error of the estimate is 0.0378 ppm.

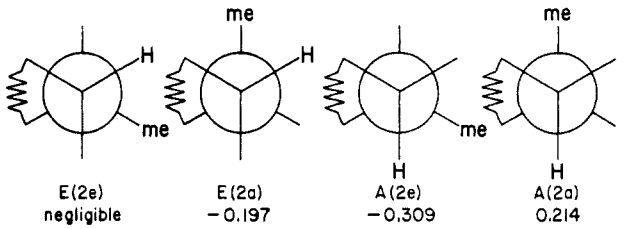


Figure 3. Comparison of the spatial and structural relationships of the four vicinal parameters. Values from the regression analysis are included.

tionships of the hydrogens with the methyl. Only the remote parameters A(3e), A(4e), and E(3a) are significant, and even these parameters show distance effects as the most remote A(4e) has the smallest magnitude. Axial methyls affect distant hydrogens more than equatorial methyls, likely due in part to ring flattening associated with axial substitution. The A(3a) methyl is large because of the spatial proximity of the methyl substituent even though it is otherwise separated from the perturbed proton by four bonds. These structurally significant shifts for axial protons cis to an axial methyl at either the 3 or 5 sites would be expected from the large effects observed in analogous carbon shifts. The parameters which were found to be insignificant statistically were either remote spatially or separated by a large number of bonds or both. Of the three parameters with magnitudes smaller than the largest residual (~0.1 ppm) A(3e) and A(4e) have been discussed. The third parameter, A(1e, 2e), may also be expected to be small since the ring distortion associated with vicinal diequatorial methyls involves only a modest steric energy (~0.9 kcal/mol). The other pairwise distortion parameter E(2a, 2e) likely is more important due to ring flattening resulting from an axial methyl. Introduction of a second methyl group geminal to an axial methyl apparently reduces the flattening since the parameters E(2a) and E(2a, 2e) are opposite in sign.

i. Origin of Vicinal Shifts. Initially the values of the four parameters for ring hydrogens with vicinal methyl groups (see Figure 3) appeared anomalous. With the exception of A(2a), which has a trans relationship to the vicinal methyl, the ring hydrogens have very similar spatial and structural relationships with the neighboring methyl group, and yet the values for these three remaining parameters given in Figure 3 vary from −0.309 to negligible. The chemical shift of a hydrogen at any site can be expected to be a sum of shifts arising from perturbations due to the neighboring groups. Treating E(parent) as the default case and cataloging only differences in substitutions at vicinal carbons as perturbations, the important neighbors are found to be the vicinal gauche C–C bonds as modified by the inductive effect of a vicinal methyl. Table IV contains the coefficients for each possible effect for these four parameters and for the parent cases, as well as the shift difference relative to E(parent) as calculated from the parameters. There is a large correlation (0.95 from a regression analysis) between the numbers of gauche C–C bonds and the shift differences. Adding the inductive effect provides a way to account for the relative values of A(2a) and A(parent). This simple explanation does not account for the large differences in E(2e) and E(2a).

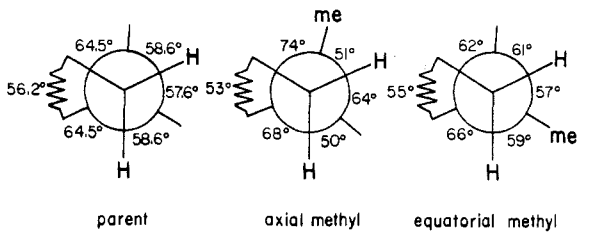


Figure 4. Comparison of the angular distortions to the cyclohexane ring induced by methyl substitution. The values are from force-field calculations from ref 13. There is little distortion due to an equatorial methyl. The axial methyl forces the vicinal ring hydrogen into closer proximity to a gauche C–C bond and an axial ring hydrogen farther away, leading to distortional corrections to coefficients for numbers of gauche C–C bonds.

Table IV. Total Shift Differences and Shift Effect Coefficients for Vicinal Sites

site	shift	$\Delta\delta$	number of C–C	coefficients		
				$\delta_{ind\text{-}G}$	$\delta_{ind\text{-}T}$	$\delta_{C\text{-}C}$
E(par)	1.642	0	0	0	0	0
E(2e)	1.632	−0.010	1	1	0	1.00
E(2a)	1.445	−0.197	1	1	0	1.10
A(2a)	1.376	−0.266	2	0	1	1.66
A(par)	1.162	−0.480	2	0	0	1.77
A(2e)	0.853	−0.789	3	1	0	2.82

The ring flattening induced by an axial methyl could be expected to modify the interactions between the vicinal gauche bonds. This angular dependence for the sake of simplicity is assumed to relate to the overlap integrals between gauche carbon bond orbitals. By use of values for the angles between ring hydrogens and vicinal gauche bonds for ref 13 (see Figure 4) and the corresponding values for the overlap integrals from Mulliken et al.,[14] the weighting coefficients for the gauche C–C bond substitutions were corrected for the angular deformations. The overlap integrals for each case were calculated with the angular correction and then normalized to the parent to give c_i:

$$c_i = OI_i/OI_{E(parent)}$$

The values of c_i range about 1.0 and the regressional parameters $\delta_{C\text{-}C}$ is given by

$$\delta_{C\text{-}C} = \sum c_i$$

(14) Mulliken, R. S.; Rieke, C. A.; Orloff, D.; Orloff, H. *J. Chem. Phys.* **1949**, *17*, 1248.

Table V. Shift Effect Parameters for Vicinal Sites

δ_{C-C}	δ_{ind-G}	δ_{ind-T}
−0.319 ± 0.053	−0.190 ± 0.111	−0.263 ± 0.149

for a summation over all relevant gauche interactions. Table IV contains the shift differences for the vicinal sites, the number of gauche C–C bonds for each site, and the coefficients for each of the shift effect parameters: δ_{C-C}, δ_{ind-G}, and δ_{ind-T}. The shift differences are linearly ordered with the angularly corrected coefficients. A linear regression fit with a multiple R of 0.9844 and a standard error of the estimate of 0.0288 ppm yielded the values for the shift effects in Table V.

Considering the rather crude estimates of angles and acknowledging that the overlap assumption is also crude, one can only be pleased with the parameters obtained for the gauche interactions and two inductive terms. The largest correlation is with δ_{C-C} but clearly the inductive terms are significant. The trans effect, δ_{ind-T}, appears in only one entry (see Table IV) and would not be well determined statistically. Additionally it is comparable, within experimental error, to the gauche inductive effect given in δ_{ind-G}. The statistical data of Table V indicate that the values for inductive effects are poorly determined, and other explanations may be possible for the 5% of the variation in the shift not accounted for by gauche C–C bonds. The effect of angular distortions upon the gauche steric interactions is documented but the absence of precise structural data on all the compounds studied prevents a final statement on this item at the present time.

ii. Prediction and Interpretation of Remaining Compounds. Using the nine structural and two distortion parameters, predicted spectra generated for 1,*cis*-i-dimethyl- (16–20), 1,*cis*-4-dimethyl- (28–30), and 1,1,4-trimethylcyclohexane (72–76) matched the corresponding experimental spectra very well, allowing otherwise tentative shift assignments to be confirmed for closely positioned resonances.

Attention is now directed to other compounds for which neither the assignments nor the conformational character can be readily designated. The three unassigned compounds, 1,1,2-trimethyl-, 1,*trans*-2,*cis*-4-trimethyl-, and 1,*cis*-2,*trans*-3-trimethylcyclohexane, with conformations of intermediate energy differences or nonchair conformations were not fit as well by using the regression analysis (see Figure 5). Spectra may be predicted for the extreme conformations (99% aee or eaa) as well as for conformations of intermediate energies (weighted averages of the extreme forms). A linear least-squares fitting routine again was used to determine the energy difference which gave the theoretical best-fit spectrum in each case.

For 1,*trans*-2,*cis*-4-trimethylcyclohexane (108–116) a good fit was found at acceptable error levels by using only a combination of higher and lower energy chair conformations (see Figure 5) properly weighted with the Boltzman factor. An analysis of the variance of the fit vs. fraction of conformation contribution (see Figure 6) indicates that only a tentative assignment of the shifts can be made for those resonances grouped in the center of the spectrum. There are three different permutations of assignments which fall within a confidence level of 75%. These three permutations of assignments involve the 3e, 5a, and 5e ring hydrogens, and thus assignments in Table II for these shifts can only be considered tentative.

Although in 1,1,2-trimethylcyclohexane (50–57) the error levels of the fit are not larger, it has previously been suggested[11] that a substantial contribution from the skew-boat conformation is likely. This is supported by a

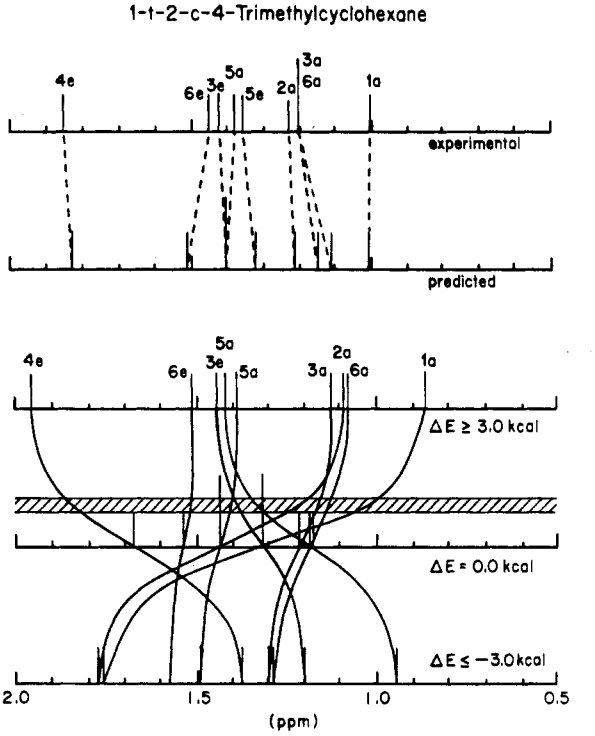


Figure 5. Analysis of 1,*trans*-2,*cis*-4-trimethylcyclohexane was performed by calculating predicted shift values for the extreme forms (99% single-chair conformation) by using the regression parameters and performing a linear least-squares best fit. The energy difference of the best fit was 1.00 kcal which is near the estimate from steric considerations. The shaded region of the figure includes the best fit within 5% error limits. The standard deviation for the predicted chemical shifts is 0.045 ppm, which is only 1.2 times the regression standard error.

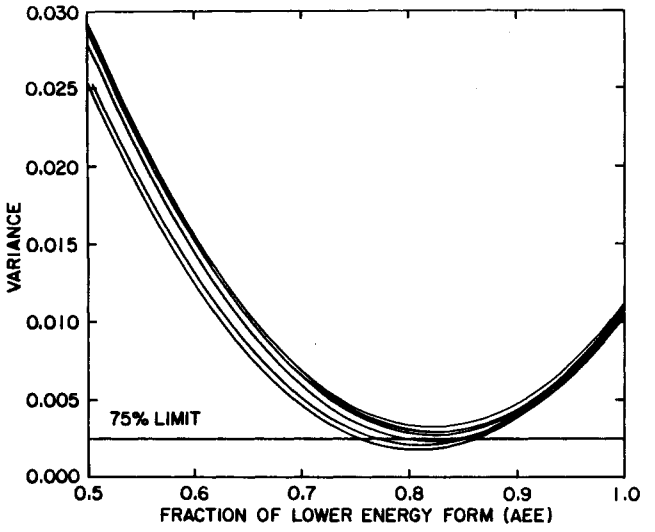


Figure 6. Plot of variance in predicted chemical shift vs. fraction of lower energy conformation for the seven permutations with lowest variance. The 75% limit is relative to the best-fit assignment. There are a total of three possible permutations in the assignment of 3e, 5a, and 5e hydrogens which fall within this limit.

similar analysis of variance and fraction of conformation contribution. For 1,1,2-trimethylcyclohexane there are 11 permutations of assignments which are within a 75% level of confidence. There are five shifts, in two groups, which give rise to the permutations of assignments, 2a and 4a, and 5a, 5e, and 6e. Therefore, the assignments for these shifts can only be considered tentative.

In 1,*cis*-2,*trans*-3-trimethylcyclohexane (86–94) the data couldn't be fit well by the parameters developed in the linear model of energetically separate chair conformations

nor by any linear combination of conformations. Only two shifts may even be assigned with any level of confidence. Since 1,*cis*-2,*trans*-3-trimethylcyclohexane has considerable steric strain energy in the extreme chair forms it is understandable that substantial difficulty might well be encountered in fitting the data with a linear model. It is likely that a skew-boat or other higher energy conformation could also make a considerable contribution to the ring hydrogen shifts in this case. In some respects the failure of the parametric set to fit this obviously distorted molecule dramatizes the success of the parameters in correlating chemical shifts of the "regular" molecules and lends confidence to the structural information which can be obtained from this method.

Conclusion

The application of ^2H natural abundance spectroscopy involves greatly simplified spectra and can aid in simplifying the process of interpretation of very complex ^1H spectra. The simple shift patterns resulting from broad-band proton decoupling due to the absence of ^2H–^2H couplings in all but a very few (0.00024%) of the molecules produce much more readily interpreted spectra. The proton-decoupled, deuterium technique supplements information obtained from the ubiquitous field of ^1H chemical shift data which is known to be rich in structural and conformational information for many compounds. When the ^1H spectral transitions are seriously banded, however, and experience large second order effects, the ^2H information is much easier to interpret. Deuterium shifts contain less error than the shift data obtained from estimating the centers of proton multiplets in highly coupled proton spectra. The structural information obtained for proton-decoupled ^2H spectra is corroborated by ^{13}C chemical shift data.[11]

The use of multiple stepwise regression analysis produced a set of empirical parameters which can be used in predicting and interpreting spectra of compounds which are either rapidly interconverting between multiple conformations or are locked in one chair conformation. Also the results suggest that nonchair conformations contribute to the structural description of certain molecules. The parameters found in this study for methylcyclohexanes which exhibit chair conformations, either rapidly interconverting between chair structures or existing solely in one extremely favored form, should prove useful in the interpretation and prediction of spectra of related compounds. Spectral deviations provide some indication of distortion in the ring system, since compounds with allegedly flattened rings would not be fit as well by the parmeter set. The use of these parameters as a tool in the interpretation of spectra of six-membered paraffin rings with substituted methyls is particularly valuable because of the importance of proximity in the effect of a methyl on a ring proton. The magnitude of these parameters provides a quantitative measure of the steric perturbations in the cyclohexane ring which provides one of the basic moieties for conformational analysis.

Vicinal substituent shifts have been rationalized in terms of the number of gauche steric interactions as modified by vicinal inductive effects. With the availability of improved spectroscopic data refined information on angular deformations could become available from these kinds of data.

Acknowledgment. This work was supported in part by the National Institutes of Health under Grant No. GM08521. Some deuterium spectra were obtained by William R. Croasmun on the Bruker-500 spectrometer at the Southern California Regional NMR facility located at the California Institute of Technology, supported by the National Science Foundation on Grant CHE 79-16324. Their assistance is gratefully acknowledged.

Registry No. Deuterium, 7782-39-0; cyclohexane, 110-82-7; methylcyclohexane, 108-87-2; 1,1-dimethylcyclohexane, 590-66-9; *cis*-1,2-dimethylcyclohexane, 2207-01-4; *trans*-1,3-dimethylcyclohexane, 2207-03-6; *cis*-1,4-dimethylcyclohexane, 624-29-3; *trans*-1,2-dimethylcyclohexane, 6876-23-9; *cis*-1,3-dimethylcyclohexane, 638-04-0; *trans*-1,4-dimethylcyclohexane, 2207-04-7; 1,1,2-trimethylcyclohexane, 7094-26-0; 1,1,3-trimethylcyclohexane, 3073-66-3; 1,1,4-trimethylcyclohexane, 7094-27-1; 1,*trans*-2,*cis*-3-trimethylcyclohexane, 1678-81-5; 1,*cis*-2,*trans*-3-trimethylcyclohexane, 7667-55-2; 1,*trans*-2,*trans*-4-trimethylcyclohexane, 7667-60-9; 1,*trans*-2,*cis*-4-trimethylcyclohexane, 7667-59-6; 1,*cis*-3,*cis*-5-trimethylcyclohexane, 1795-27-3; 1,*cis*-3,*trans*-5-trimethylcyclohexane, 1795-26-2.

Iminium Ion Mediated Cyclizations with 4-Aryl-1,4-dihydropyridines. Bridging with Thiophene and Furan

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Treatment of [(2-thienyl)phenyl]-, [(3-thienyl)phenyl]-, [((2-thienyl)methyl)phenyl]- and [2-(furylmethyl)-phenyl]-1,4-dihydropyridines with aluminum chloride afforded products derived from intramolecular trapping of the dihydropyridine/iminium ion by the heterocycle. These products were either monocyclized, from heterocyclic attack on the iminium ion followed by rearomatization of the heterocycle, or biscyclized, from trapping of an electrophilic substitution intermediate in a second intramolecular reaction.

The therapeutic utility of 4-aryl-1,4-dihydropyridines as cardiovascular agents has been widely recognized.[1] Mechanistically, these molecules act to inhibit contractility in cells by antagonizing the movement of calcium ions through the slow calcium channels[2] in the cell membrane. Concomitant with clinical success, a renewed interest in the chemistry of this class of compounds is evident.[3-9]

The suggestion that biological activity within the 4-

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(3) Meyer, H.; Wehinger, E.; Bossert, F.; Stoepel, K.; Vater, W. *Arzneim.-Forsch.* **1981**, *31*, 1173.

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