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Ab Initio IGLO Studies of the Conformational and Substituent Dependencies of α-, β-, γ-, and δ-Effects in the ^{13}C NMR Spectra of 1-Substituted Butanes

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Abstract: Ab initio IGLO (individual gauge for localized molecular orbital) methods of SCF-MO theory are used to extend studies of the conformational dependencies of isotropic ^{13}C chemical shifts to include δ-effects. All of the ^{13}C chemical shifts in butane and the 1-substituted butanes $CH_3CH_2CH_2CH_2X$ (X = CH_3, CN, OH, F) are obtained as functions of the torsion angles about the C1−C2 (φ_1) and C2−C3 (φ_2) bonds with structures optimized at the HF/6-31G* level. The calculated ^{13}C chemical shifts, averaged over the two dihedral angles, compare favorably with the experimental data. In contrast to calculated β-effects, which are almost independent of φ_2, α-, γ-, and δ-effects depend on both dihedral angles. The similarities in the surface and contour plots for each of the effects suggest a positional dependence, while the surface elevations are primarily determined by the nature of the substituent. The calculated stereochemical dependencies of β-, γ-, and δ-effects compare favorably with the experimental results in substituted *trans*-decalins and bicyclo[2.2.1]heptanes over a wide range of torsion angles. For all substituents the δ-effects assume their largest values for *syn*-axial (g^+g^-/g^-g^+) conformations, and γ-*gauche* effects in these arrangements are 4−5 ppm deshielded in comparison with g^+g^+ and g^+t conformations. Analyses of the IGLO local bond contributions show that the C−H bonds pointing toward and away from the substituent are primarily responsible for the deshielding of the δ-carbon in *syn*-axial arrangements and appear to be independent of compression of the proximate Cδ−H bond.

I. Introduction

Substituent effects[1] in the ^{13}C NMR spectra of aliphatic and alicyclic compounds are of interest in the use of NMR techniques for structural and conformational studies.[2] In these applications extensive use has been made of *empirical additivity relationships*. It was noted[1] that ^{13}C chemical shifts for aliphatic and alicyclic hydrocarbons could be described by an empirical equation for which a typical form is[3−6]

$$\delta_C = n_\alpha\langle\Delta\delta_\alpha\rangle + n_\beta\langle\Delta\delta_\beta\rangle + n_\gamma\langle\Delta\delta_\gamma\rangle + n_\delta\langle\Delta\delta_\delta\rangle + S \quad (1)$$

where n_α, n_β, n_γ, and n_δ denote the number of substituents at α-, β-, γ-, and δ-positions having additivity increments $\langle\Delta\delta_\alpha\rangle$, $\langle\Delta\delta_\beta\rangle$, $\langle\Delta\delta_\gamma\rangle$, and $\langle\Delta\delta_\delta\rangle$, respectively. The term S is said to be a "steric factor" determined by the extent of branching at both the carbon of interest and its adjacent carbons. In the compilations of empirical data for aliphatic compounds $\langle\Delta\delta_\alpha\rangle$ and $\langle\Delta\delta_\beta\rangle$ are large and almost always positive, $\langle\Delta\delta_\gamma\rangle$ are invariably negative ranging from −1.5 to −7.2 ppm, and δ-effects $\langle\Delta\delta_\delta\rangle$ range from +0.3 to −1.4 ppm.[4,5] Longer range substituent effects have been reported but have not typically been used in such analyses as they may arise entirely from substituent-induced changes of the molecular geometry. The empirical estimation of chemical shifts via eq 1 does not usually include conformational effects. As a consequence, eq 1 is not applicable for multicyclic hydrocarbons.[7] Exceptions are γ-effects in *gauche* and *trans* (or *anti*) arrangements for which there is an extensive literature.[1,2,7−12] The sensitivity of ^{13}C chemical shifts to stereochemistry offers promise for conformational studies in complex molecules.

Previous studies from this and other laboratories[8−13] have used ab initio MO methods to examine the conformational dependencies of ^{13}C chemical shifts as well as the α-, β-, and γ-effects in cyclic and acyclic hydrocarbons.[8−10] Calculated results for the angularly dependent γ-effects based on a butane/propane model were qualitatively consistent with the experimental observations. A more detailed comparison of the IGLO results for the torsion angle dependence of γ-effects with experimental data showed that the simple model based on butane and propane was not quantitatively applicable to cyclic molecules.[8] The use of model compounds with branching along the chain[9] led correctly to γ-effects of positive sign in *anti* arrangements (φ = 180°) and asymmetry in the plots (about *anti* arrangements) associated with different stereochemistry.[14] The calculated results for the 2,3-dimethylbutane/2-methylbutane model were

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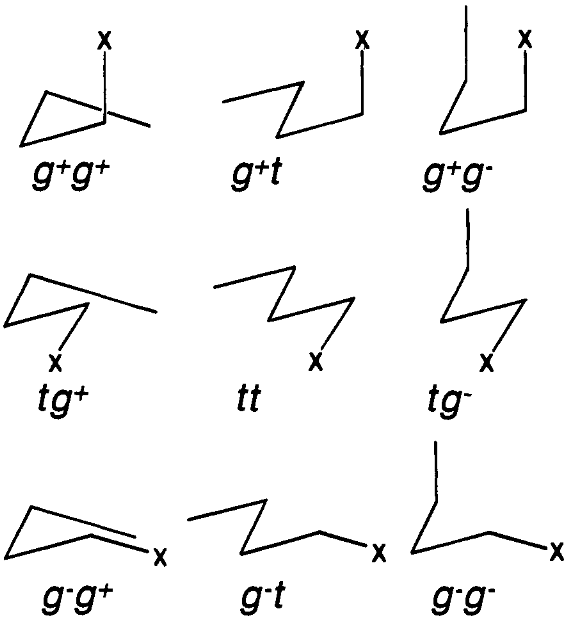

Figure 1. Schematic representations of the nine standard arrangements for the C−C−C−C−X moiety in cyclic molecules.

in agreement with the experimental values in dimethyl-*trans*-decalin compounds and bicyclo[2.2.1]heptanes. To investigate the effects of ring strain on ^{13}C chemical shifts, the α-, β-, and γ-effects for the cyclobutane ring carbons due to −CN, $-CH_3$, and −F substituents were examined as a function of ring pucker angle,[10] and these results led to reasonable predictions of the ^{13}C chemical shifts in strained bicyclo[*n.m.*1]alkanes. Conformational studies such as these offer promise of a generalization of eq 1 to include multicyclic compounds and polymers.

From experimental studies of δ-effects[15–20] in cyclic molecules it was concluded that these can be used for stereochemical assignments. Typically, δ-effects in *trans*-decalols and steroids are less than 1 ppm and can be either to high or low frequency. Because larger shifts of 2−3 ppm to higher frequency appear to be unique to the *syn*-axial (g^+g^- or g^-g^+) conformations depicted in Figure 1, it was suggested that the OH··CH_3 interactions were the dominant factor. However, deshielding effects in these arrangements[18] could not be reconciled in terms of the well-known *steric compression model*,[21,22] because this model had been introduced to explain the *shielding* at the C4 carbon atom in *gauche* arrangements of butane moieties. The stereochemical dependencies of δ-effects have also been useful in NMR studies of steroids,[23–27] but these effects may be substantially influenced by the size of adjacent substituents.[27] Not surprisingly, such measurable δ-effects are not unique to bicyclic molecules since they appear in acyclic molecules,[28] ortho-substituted toluenes,[29] and other ring systems.[30–32]

The computational methods for molecular structures and chemical shielding are presented in the next section. In section III the calculated ^{13}C isotropic chemical shifts for butane and the four substituted butanes are compared with the experimental data. A slight improvement is noted in the calculated chemical shifts on averaging over the torsional modes using the angularly dependent chemical shifts and energies. In section IV the calculated conformational dependencies of the α-, β-, γ-, and δ-effects for each of the four substituents are depicted by surface and contour plots. The calculated results are then compared with the available experimental data for a series of "rigid" bicyclic molecules. In section V the IGLO local bond contributions are used to examine electronic factors associated with γ- and δ-effects.

II. Computations

A. Molecular Structures. All geometries are optimized ones using Gaussian 86,[33] or Gaussian 90[34] codes with split valence basis sets and polarization functions at the HF/6-31G* level.[35] Initially, smaller basis sets (HF/3-21G) were used for geometry optimizations but the shielding results (especially for the molecules with heteroatoms) were found to be extremely dependent on the quality of the basis sets used for the geometry optimizations. The sensitivity of chemical shielding to geometrical factors is consistent with observations of others,[36–40] and it is now clear that energy optimized geometries are almost always essential for good quality shielding calculations.

Calculations for butane (**1**), pentane (**2**), pentanenitrile (**3**), 1-butanol (**4**), and 1-fluorobutane (**5**) were performed at 60° intervals of the dihedral angles φ_1 and φ_2. All geometries are fully optimized (except for the two dihedral angles) at the HF/6-31G* level. For each of the substituted butanes the 60° grid requires 36 structures but only 20 were actually calculated as the rest followed by symmetry. The additional symmetry of butane and pentane molecules further reduced the number

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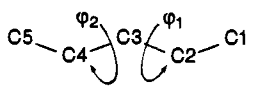

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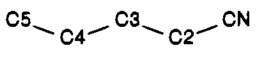

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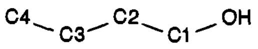

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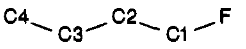

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of data points required. The use of such a coarse grid is not usually desirable, but the use of a 30° grid would have quadrupled the computational time. Furthermore, most of the experimental data occur for molecules having dihedral angles fairly close to the angles in the 60° grid.

Energy optimized structures for butane (**1**) and pentane (**2**) have been reported previously with basis sets of comparable or better quality.[41-44] The major improvement on introducing correlation effects into the calculations for the hydrocarbons appears to be the reduction of the energies of the *g*, g^+g^+, g^+g^-, etc. conformations relative to the *trans* arrangements.

The lowest energy conformations of pentane and pentanenitrile are those in which the non-hydrogen atoms are all *trans* ($\varphi_1 = \varphi_2 = 180°$), whereas 1-butanol and 1-fluorobutane have global minima in *gt* arrangements with φ_1 and φ_2 near 60° and 180°, respectively. The calculated differences (HF/6-31G*) between the *gt* and *tt* conformations in the series **2**−**5** are 0.946, 0.181, −0.160, and −0.361 kcal/mol, respectively. The appearance of global minima in *gauche* arrangements of O−C−C−C in 1-propanol and 2-butanol has recently been examined by Houk and co-workers,[45] and questions of how the electronegativity influences the strengths of *gauche* effects are of current interest.[46-48]

B. Shielding Calculations. All shielding calculations in this study were based on the IGLO (individual gauge for localized orbitals) formulation of Kutzelnigg et al.[36,37] This procedure has been applied with good success to a large number of molecules having elements in the first through third rows. In this method localized MO's, which are associated with inner shells, bonding orbitals, and lone pairs, have unique gauge origins for the calculation of diamagnetic and paramagnetic terms. Distributed origins algorithms such as IGLO, LORG, and GIAO provide a satisfactory description of chemical shielding using modest basis sets.[36-39] In the notation of the Bochum group[36,37] Basis Set II is a (9/5) set contracted to a triple-ζ (51111/2111) set with one set of (5) d-type functions on elements C−F and for hydrogen a (311) set with p-type polarization functions.[49] All IGLO calculations here were performed with Basis Set II′ which differs from Basis Set II in using a double-ζ set on hydrogen. The ^{13}C shielding results with the two basis sets are comparable. There have been extensive studies of the basis set dependence of chemical shielding.[36-39] A previous related study,[10] for example, presented results for several substituted cyclobutanes in terms of IGLO Basis Sets I, II′, and II. As usual, calculated results improved with basis set quality and there is substantial improvement for the triple-ζ set II′ in comparison with the double-ζ set (Basis Set I). Since there is only small improvement for Set II in comparison with II′, the latter set was adopted for the large number of computations required here. All chemical shifts were obtained by subtracting the chemical shielding for the nuclei of interest from the reference compound shielding. The ^{13}C shielding of the reference compound tetramethylsilane (TMS) was not calculated. The computed methane shielding value (201.0 ppm for Basis Set II′ and a HF/6-31G* geometry) and the experimental chemical shift (−2.3 ppm)[50] lead to a TMS reference value of 198.7 ppm. All computations were performed using Convex C220, C240 minisupercomputers, or Digital Equipment Corp. workstations. The 3D surface plots and contour plots were generated by a commercial plotting package which includes 2D and 3D spline algorithms (cubic or bicubic spline interpolation).[51] Molecular mechanics calculations for substituted *trans*-decalins, bicyclo[2.2.1]heptanes, and bicyclo[2.2.2]octanes were based on the MMX force field derived from Allinger's MM2 force field[52] in the PCMODEL program.[53]

In the previous studies[7-10] of conformational dependencies of chemical shifts it was noted that the ^{13}C isotropic shielding data could be represented accurately by means of Fourier series expansions. The extension of these to situations with two angles is

$$\delta(\varphi_1,\varphi_2) = \sum_{n=0,m=0} A_{\mathrm{nm}} \cos(n\varphi_1)\cos(m\varphi_2) \qquad (2)$$

where the coefficients A_{nm} can be determined by linear regression analyses of the calculated shielding data. Equation 2 was applied to all of the substituent effect data described herein. Except for β-effects, the results are not included because the standard deviations for the linear regression analyses were typically of the order of 1 ppm with as many as 15 terms in the expansion. For butane and the 1-substituted butanes the conformationally averaged shifts $\langle\delta_i\rangle$ are calculated as the average of the chemical shift surface $\delta_i(\varphi_1,\varphi_2)$ over the corresponding energy surface $E_i(\varphi_1,\varphi_2)$,

$$\langle\delta_i\rangle = \int \delta_i(\varphi_1,\varphi_2)e^{-E_i(\varphi_1,\varphi_2)/kT}\,d\varphi_1\,d\varphi_2 \Big/ \int e^{-E_i(\varphi_1,\varphi_2)/kT}\,d\varphi_1\,d\varphi_2 \qquad (3)$$

The averaged chemical shifts in the next section were obtained by numerical integration of eq 3. For very small molecules it would be feasible to vary all of the internal degrees of freedom and calculate the chemical shifts by averaging over each of the these. For even the small molecules in this study this number of computations would be astronomical.

The use of fully optimized structures subject only to the dihedral angle constraints presents problems in the interpretation of the chemical shifts because the remaining $3N - 8$ internal degrees vary in each structure. Clearly, this leads to uncertainties in separating the importance of the two dihedral angles from the concomitant changes in bond lengths, internal angles, and other dihedral angles.[54] On the other hand, constraining certain bond lengths and angles leads to unphysical values of energies and chemical shifts. For example, calculations were performed for the model compounds pentane and butane at the Basis Set II′ level with a standard geometrical model (e.g., tetrahedral angles and all $r_{\mathrm{CH}} = 1.084$ Å). The 18.3 ppm calculated δ-effect in the *syn*-axial arrangement is an order of magnitude larger than experimental values and those based on relaxed geometries!

III. Comparisons of Calculated Chemical Shifts and Substituent Effects for Pentane and the 1-Substituted Butanes with Experimental Values

Entered in the third column of Table 1 are the calculated IGLO (Basis Set II′) isotropic ^{13}C chemical shifts $\delta_i^{\min}$ for butane

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Table 1. Comparison of Calculated Chemical Shifts (IGLO Basis Set II′) Averages for Butane and Substituted Butanes (HF/6-31G* Optimized Geometries) with Solution NMR Data[a]

			$\langle \delta_i \rangle$		$\langle \Delta\delta_i \rangle$		
compd	carbon	$\delta_i^{\min}$	calcd	expt	calcd[b]	expt[b]	empirical[c]
n-butane[d,e]	C1	17.2	16.5	13.55			
	C2	27.0	25.9	24.82			
	C3	27.0	25.9	24.82			
	C4	17.2	16.5	13.55			
n-pentane[d,f]	C1	17.2	16.6	13.87			
	C2	25.8	24.4	22.33	7.9	8.78	9.1
	C3	35.2	34.0	34.18	8.1	9.36	9.4
	C4	25.8	24.4	22.33	−1.5	−2.49	−2.5
	C5	17.2	16.6	13.87	0.1	0.32	0.3
pentanenitrile[g]	C1	19.0	18.3	16.89	1.8	3.34	3.1
	C2	30.5	29.4	28.06	3.5	3.24	2.4
	C3	25.1	23.3	22.28	−2.6	−2.54	−3.3
	C4	16.6	15.9	13.41	−0.6	−0.14	−0.5
	CN	125.8	125.9	120.05			
1-butanol[h]	C1	60.5	59.9	61.7	43.4	48.2	49.1
	C2	33.8	33.3	35.3	7.4	10.5	10.1
	C3	21.8	20.9	19.4	−5.0	−5.4	−6.2
	C4	16.9	16.6	13.9	0.1	0.4	0.3
1-fluorobutane[d,i]	C1	79.7	79.1	83.63	62.6	70.08	70.1
	C2	33.7	33.0	32.39	7.1	7.57	7.8
	C3	21.4	20.6	18.31	−5.3	−6.51	−6.8
	C4	16.7	16.2	13.40	−0.3	−0.15	0.0

[a] All values in ppm referenced to TMS. [b] These values are obtained by subtracting the butane chemical shifts from those of the substituted butanes. [c] Reference 4. [d] Measured (butane, pentane, fluorobutane) in $CDCl_3$ relative to TMS.[30] [e] Minimum energy (6-31G*): −157.298 409 6 hartrees at $\varphi = 180°$. [f] Minimum energy (6-31G*): −196.333 096 5 hartrees at $\varphi_1 = \varphi_2 = 180°$. [g] Syntheses: Barfield, M.; Conn, S. A.; Marshall, J. L.; Miiller, D. E. *J. Am. Chem. Soc.* **1976**, *98*, 6253−60. ^{13}C shifts: Barfield, M., unpublished results, 1974. Minimum energy (6-31G*): −249.027 239 8 hartrees at $\varphi_1 = \varphi_2 = 180°$. [h] In acetone-$d_6$ relative to internal TMS by: Marshall, J. L.; Conn, S. A.; Barfield, M. *Org. Magn. Reson.* **1977**, *9*, 404−407. Minimum energy (6-31G*): −232.145 347 1 hartrees at $\varphi_1 = 63.52°$, $\varphi_2 = 180.21°$. [i] Minimum energy (6-31G*): −256.147 416 8 hartrees at $\varphi_1 = 61.19°$, $\varphi_2 = 180.66°$.

(**1**), pentane (**2**), pentanenitrile (**3**), 1-butanol (**4**), and 1-fluorobutane (**5**) in their lowest energy conformations (HF/6-31G*). The experimental ^{13}C chemical shifts are given for comparison. The average deviation between the calculated and experimental values is 2.5 ppm for all 16 distinct carbons not including the CN carbon of the nitrile **3** and the C1 carbon of fluoro compound **5**. Differences (−5.8 and 4.0 ppm, respectively) between the calculated and experimental values for these two carbons are much larger than any others in this series. These differences follow the same trends (−4.6 and 6.1 ppm, respectively) which were noted for the analogous carbons in the cyclobutane series.[10] The optimized geometries around the nitrile and fluoro groups are particularly sensitive to basis set quality. It seems likely that these disparities would be partially reduced by performing the geometry optimizations with larger basis sets and by introducing the effects of electron correlation. Moreover, adequate descriptions of nitrogen and fluorine shieldings invariably require larger basis sets than the ones used here, and it appears to be generally true that shielding results for atoms bonded to these atoms are also sensitive to basis set quality. Electron correlation effects are important for shielding of molecules which have multiple bonds, e.g., the nitrile function.[55]

The IGLO ^{13}C chemical shifts for the substituted butanes in their minimum energy conformations are not in as good agreement with the experimental values as the substituted *cyclo*butanes obtained with the same basis set.[10] One possibility is that torsional averaging about the several C−C single bonds in the substituted butanes may be more important than the pucker angle averaging in the cyclobutanes. To investigate the importance of the torsional motions, the average ^{13}C shifts for the carbons in **1**−**5** were obtained by two-dimensional numerical integration using eq 3 (at 300 K), the chemical shift surfaces $\delta_i(\varphi_1,\varphi_2)$ for each of the carbons, and the HF/6-31G* torsion potential energy data $E_i(\varphi_1,\varphi_2)$. The averaged chemical shifts $\langle \delta_i \rangle$ are entered in the fourth column of Table 1. Averaging decreases the calculated results by as much as 1.8 ppm. Since the $\delta_i^{\min}$ values (with three exceptions) are larger than the experimental solution values, torsional averaging improves the overall agreement between calculated and experimental results. If the CN carbon of **3** and the C1 carbon of **5** are again not included, torsional averaging reduces the average deviation between the calculated and experimental results to 1.8 ppm. This is still a larger discrepancy than for the substituted cyclobutanes.[10] From the data in Table 1 it can be seen that torsional averaging is more important for the interior (C2, C3, and C4 carbons of pentane, for example) carbons than for the terminal (C1 and C5) carbons. It seems likely that the agreement between the calculated and experimental chemical shifts would be further improved by averaging over the C4−C3−C2−X and C3−C4−C5−H torsional motions.

In Table 1 are included the calculated and experimental values for the α-, β-, γ-, and δ-effects $\langle \Delta\delta_i \rangle$ for each of the four substituents. The calculated values were obtained from the torsion averaged values $\langle \delta_i \rangle$, but the results based on $\delta_i^{\min}$ are comparable. In the last column are given the empirical values which are often used in eq 1. Except for the $\langle \Delta\delta_\alpha \rangle$ associated with the hydroxyl and fluoro substituents, the agreement is fairly good considering that the calculated data are appropriate to isolated molecules. Gas to solution shifts of several parts per million[37] are compensated, in part, by indirectly referencing to the measured shift for methane in solution. Since the substituent effects to be described in the next sections represent chemical shift *differences* between very similar molecules, differential medium effects are expected to be much less important.

IV. Conformational and Substituent Dependencies of α-, β-, γ-, and δ-Effects

The calculated α-, β-, γ-, and δ-effects $\Delta\delta_i(\varphi_1,\varphi_2)$ of the four substituent groups in **2**−**5** were obtained by subtracting the IGLO shielding results $\sigma_i(\varphi_1,\varphi_2)$ for the C1−C4 (C2−C5 for **2** and **3**) carbons from the corresponding butane values. All shielding data were obtained with Basis Sets II′ using energy optimized structures (HF/6-31G* level) at 60° grids of the two dihedral angles. Because of the particular interest here, the IGLO based γ- and δ-effects are given in Table 2. The α- and β-effect results are given in the supplementary material. Spline algorithms[51] were used to interpolate points at 10° intervals of the dihedral angles for use in constructing the surface and contour plots. The α-, β-, γ-, and δ-methyl substituent effects, which were based on the pentane and butane IGLO shielding results, are plotted as functions of the two dihedral angles in Figure 2, plots a−d, respectively. The corresponding surface and contour plots for substituent effects of nitrile, hydroxy, and fluoro substituents are given in Figures 3−5.

The IGLO results for conformationally averaged substituent effects in Table 1 are in reasonable agreement with the experimental data. With increasing substituent electronegativity (neglecting the nitrile data) the averaged α-effects increase substantially, the β-effects decrease slightly, the γ-effects become more negative, and the δ-effects display no clear trend. Trends for particular conformations may differ. To compare the calculated with the observed dependencies it is necessary to find chemical shift data for suitably rigid compounds with each of the four substituents. Unfortunately, most compounds

Table 2. IGLO Results for Conformational Dependencies of γ- and δ-Effects for *n*-Pentane, Pentanenitrile, 1-Butanol, and 1-Fluorobutane/Butane[a]

			$\Delta\delta_\gamma$[c]					$\Delta\delta_\delta$[c]			
φ_1	φ_2	δ(C3)[b]	$-CH_3$	$-CN$	$-OH$	$-F$	δ(C4)[b]	$-CH_3$	$-CN$	$-OH$	$-F$
0	0	17.5	2.9	1.6	1.7	0.9	14.2	1.9	0.1	1.9	1.5
	60	24.5	−2.5	−2.1	−3.1	−3.6	13.8	2.9	0.1	2.3	1.9
	120	26.8	−11.1	−7.7	−14.9	−14.5	18.3	0.7	0.0	0.5	0.2
	180	27.5	−7.3	−4.2	−8.8	−8.7	17.3	0.2	−0.7	−0.3	−0.5
60	0	17.9	0.8	0.0	0.2	−0.3	12.0	2.0	0.6	0.5	0.0
	60	24.2	−4.3	−3.7	−5.6	−5.6	14.4	−0.5	−0.5	−0.6	−0.7
	120	23.5	−4.2	−2.6	−4.7	−4.7	17.9	0.2	−0.4	−0.2	−0.3
	180	27.0	−4.5	−3.8	−5.5	−5.6	17.2	0.1	−0.7	−0.3	−0.5
	240	23.5	−3.8	−2.4	−4.0	−4.1	17.9	0.7	0.0	0.4	0.4
	300	24.2	0.3	−0.2	0.1	−0.7	14.4	2.6	0.7	2.4	2.0
120	0	17.5	0.1	−0.5	3.8	−0.8	14.2	0.2	−0.4	2.0	−0.2
	60	24.5	−0.4	−0.9	−1.1	−1.6	13.8	0.6	0.0	1.0	0.8
	120	26.8	−0.7	−0.7	−2.2	−3.0	18.3	0.2	−0.1	0.2	0.2
	180	27.5	−0.8	−1.1	−2.2	−3.1	17.3	0.0	−0.6	−0.3	−0.5
	240	26.8	−0.6	−0.5	−2.2	−4.0	18.3	0.6	−0.2	0.0	−0.1
	300	24.5	−0.1	−0.8	−1.8	−2.8	13.8	0.0	−0.3	−0.1	−0.2
180	0	17.9	0.3	−0.6	−1.7	−2.3	12.0	0.3	−0.3	−0.3	−0.6
	60	24.2	−0.3	−1.2	−3.4	−4.2	14.4	0.6	−0.2	0.9	0.7
	120	23.5	−1.0	−1.8	−6.0	−7.8	17.9	0.2	−0.2	0.1	0.0
	180	27.0	−1.1	−1.9	−5.9	−7.5	17.2	0.0	−0.6	−0.3	−0.5

[a] Angles in degree, chemical shifts ppm relative to TMS, and substituent effects in ppm. [b] Calculated ^{13}C isotropic chemical shifts for butane. [c] The γ- and δ-effects $\Delta\delta_i$ are the differences between the values obtained for the **2**−**5** and the corresponding values for the C3 and C4 carbons of butane.

for which ^{13}C NMR data are available are highly branched around some of the carbons. Branching effects are quite important and will be discussed in more detail in the next section. Table 3 presents a comparison of the IGLO substituent effects with the available experimental data for several substituted bicyclic molecules having the substituents $-CH_3$, $-CN$, $-OH$, and $-F$. There are fewer entries for molecules with nitrile and fluorine groups included in this study as they often provide extremes for the influence of substituent effects. Data in Table 3 apply to molecules substituted with two or more substituents and include 1-substituted bicyclo[2.2.2]octanes (BO), 1- and 2-substituted *trans*-decalins (TD), and 2-substituted bicyclo[2.2.1]heptanes (BH). The estimated dihedral angles in Table 3 apply to the methyl-substituted compounds. The values reported here are those in the 5° spline interpolation tables which are closest to the molecular mechanics results.[52,53] For purposes of comparison in the next section, molecular geometries for other substituents were assumed to be identical. Since the experimental data for the 1-substituted compounds involve quaternary carbons, they are poor examples for comparison with the substituted butane data. From the analysis of branching effects in the next section the only cases in Table 3 for which agreement might be expected are those for the γ- and δ-carbons of the *trans*-decalins.

A. Comparisons with Substituent Dependencies in Cyclic Molecules. This section includes discussions of the similarities in the conformational dependencies of the four substituents and comparisons of calculated and experimental results for several series of substituted bicyclic molecules. This is followed by detailed comparisons of the calculated and experimental conformational/branching dependencies in "rigid" methyl- and hydroxy-substituted bicyclic compounds.

1. α-Effects. Figures 2a−5a show surface and contour plots for α-effects of the $-CH_3$, $-CN$, $-OH$, and $-F$ functional groups, respectively. Although the $\Delta\delta$ magnitudes vary considerably with substituent, the four plots are similar in shape and cover comparable ranges. In all four of the surface plots the absolute minima occur at $\varphi_1 = 0°$ and $\varphi_2 = 120, 240°$ and the absolute maxima occur at $\varphi_1 = \varphi_2 = 0°$. Changes in the surface and contour plots with substituents are as follows: the maxima and minima in the interior region become more pronounced. For the methyl-substituent effects in Figure 2a the surface regions have little structure between $120° < \varphi_1 < 240°$. Although the effect of a nitrile group in Figure 3a leads to different values than the other three substituents, the positions of the maxima and minima are similar. The relative maxima and minima in the surface plots for the hydroxyl and fluoro substituents become even more pronounced in Figures 4a and 5a.

The surface elevations in Figures 2a−5a depend strongly on the nature of the substituent, e.g., substituent electronegativity. It is not surprising that the very large predicted increases of $\Delta\delta_\alpha$ with substituent electronegativity are reproduced by the experimental data in Table 3. While calculated α-effects for the first two entries (1-substituted *trans*-decalins) are particularly poor in being 12−16 ppm greater than the experimental data, the average deviation is 2.7 ppm for the remaining 15 items in Table 3.

Slices taken through the α-, β-, and γ-effect surfaces for $\varphi_2 = 0°$ and 180° in Figures 2−5 are symmetrical about $\varphi_1 = 180°$ and have similar shapes. Two-dimensional slices taken through the surface plots at $\varphi_2 = 180°$ in Figure 2a−c resemble the corresponding IGLO α-, β-, γ-effect plots for the butane/propane model.[8,9] However, the slices taken through the surface and contour plots of α- and γ-effects (in contrast to β-effects) are quite unsymmetrical for all other values of φ_2. For a given substituent the α- and γ-surfaces and contours have similar shapes. There is also a fairly good (and unsuspected) linear correlation of the calculated $\Delta\delta_\alpha$ and $\Delta\delta_\gamma$,

$$\Delta\delta_\alpha = a\Delta\delta_\gamma + b \qquad (4)$$

where for $-CH_3$, $-CN$, $-OH$, and $-F$ the respective slopes (standard deviations) a are 0.77 (0.03), 0.60 (0.02), 0.73 (0.04), and 0.83 (0.05) and intercepts b are 9.6, 3.6, 47.7, and 68.0 ppm. The latter are essentially the differences between the calculated $\langle\Delta\delta_\alpha\rangle$ and $\langle\Delta\delta_\gamma\rangle$ in Table 1. The ubiquity of the conformational features in Figures 2−5 implies that *conformational dependencies* are more sensitive to *positional* than *electronic* features of the substituents.

2. β-Effects. Plots of the β-effects $\Delta\delta_\beta(\varphi_1,\varphi_2)$ in Figures 2b−5b also fall within a range of about 15 ppm. Again, there

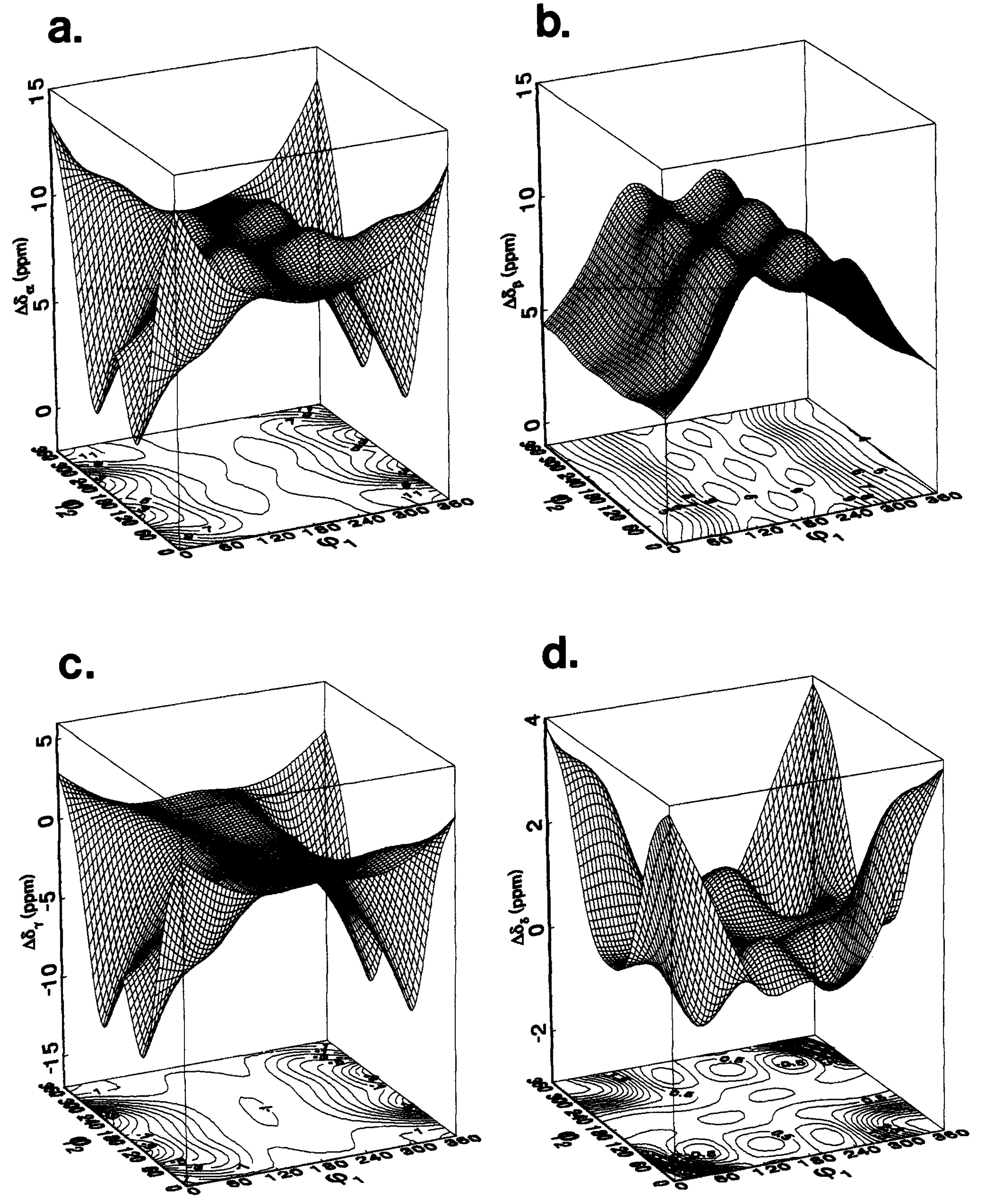

Figure 2. Calculated (IGLO Basis Set II′, HF/6-31G*) surface and contour plots of substituent effects $\Delta\delta_i$ in ppm for each of the carbons in pentane (**2**) plotted as a function of the dihedral angles φ_1 and φ_2, measured about the C2−C3 and C3−C4 bonds, respectively: (a) $\Delta\delta_\alpha(\varphi_1,\varphi_2)$, the contour lines are separated by 1 ppm; (b) $\Delta\delta_\beta(\varphi_1,\varphi_2)$, the contour lines are separated by 0.5 ppm; (c) $\Delta\delta_\gamma(\varphi_1,\varphi_2)$, the contour lines are separated by 1 ppm; and (d) $\Delta\delta_\delta(\varphi_1,\varphi_2)$, the contour lines are separated by 0.25 ppm.

are substantial similarities among the four plots, including relatively little dependence on the dihedral angle φ_2. The β-effects increase monotonically by 5−6 ppm with increasing φ_1. Maxima are predicted near 120° and 240°. All β-effect surfaces have troughs centered at φ_1 = 180°, which become substantially deeper in proceeding from CH_3 to F. A linear regression analysis of the calculated data for pentane/butane leads to a result of the form of eq 2,

$$\Delta\delta_\beta = -2.48\ \cos\varphi_1 - 1.01\ \cos 2\varphi_1 + 7.4\ \text{ppm} \qquad (5)$$

with r^2 = 0.96 and the standard deviation 0.5 ppm. With only

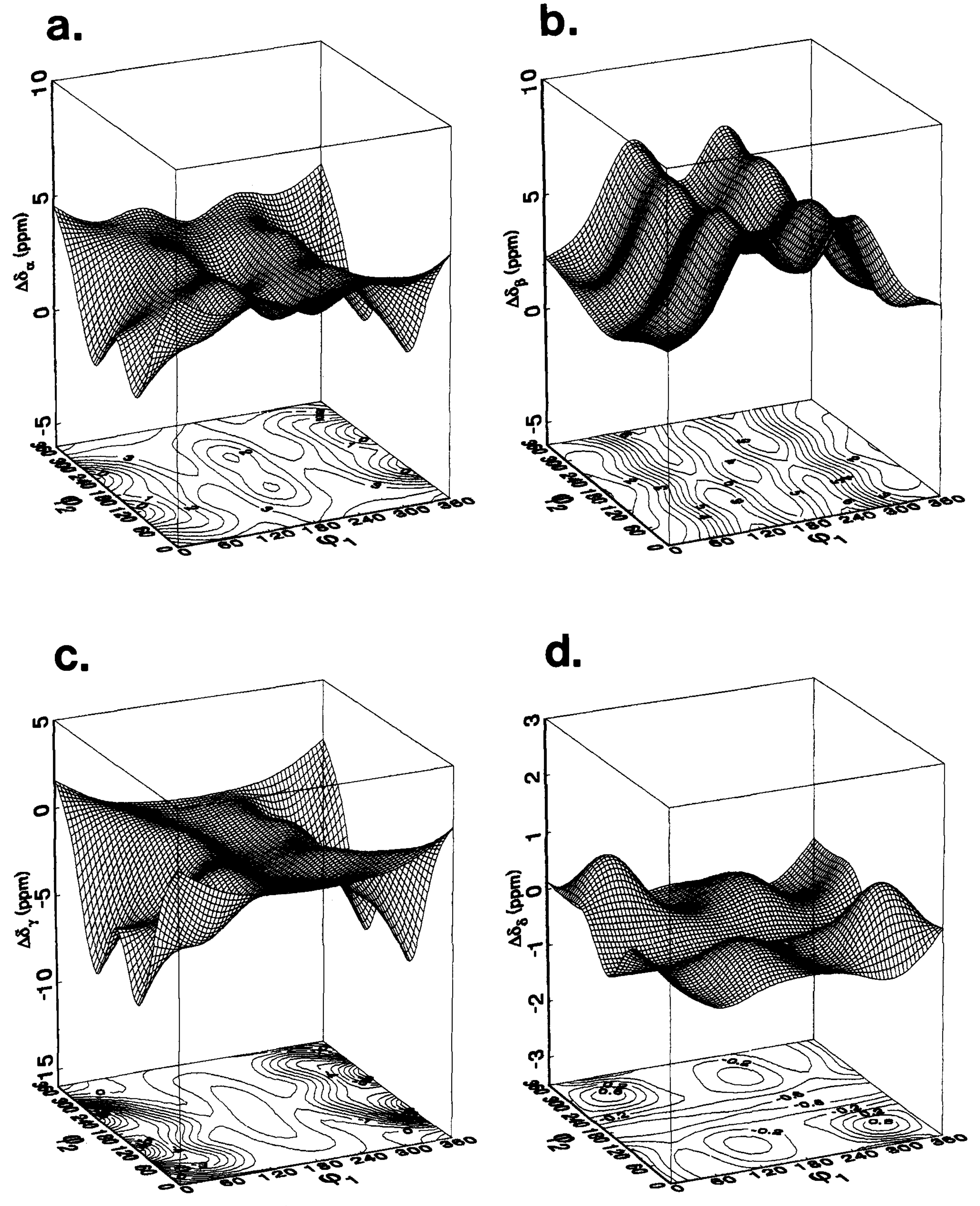

Figure 3. Calculated (IGLO Basis Set II′, HF/6-31G*) surface and contour plots of substituent effects $\Delta\delta_i$ in ppm for each of the carbons in pentanenitrile (**3**) plotted as a function of the dihedral angles φ_1 and φ_2, measured about the C2−C3 and C3−C4 bonds, respectively: (a) $\Delta\delta_\alpha(\varphi_1,\varphi_2)$, the contour lines are separated by 0.5 ppm; (b) $\Delta\delta_\beta(\varphi_1,\varphi_2)$, the contour lines are separated by 0.5 ppm; (c) $\Delta\delta_\gamma(\varphi_1,\varphi_2)$, the contour lines are separated by 0.5 ppm; (d) $\Delta\delta_\delta(\varphi_1,\varphi_2)$, the contour lines are separated by 0.2 ppm.

three terms the analogous expressions are not quite as good for β-effects of −CN, −OH, and −F substituents.

The calculated $\Delta\delta_\beta$ for the 1-substituted butanes are compared in Table 3 with the experimental data in several series of substituted bicyclic molecules. Unfortunately, data for compounds with −CN and −F substituents are not available for each set of data, but there are some interesting correlations between the calculated and experimental results. The predicted order of β-effects is conformation dependent. In the series of 1-substituted bicyclooctanes the order is $-CH_3 > -OH > -F > -CN$ in both the calculated and experimental data.

3. γ-Effects. Surface and contour plots of $\Delta\delta_\gamma(\varphi_1,\varphi_2)$ for

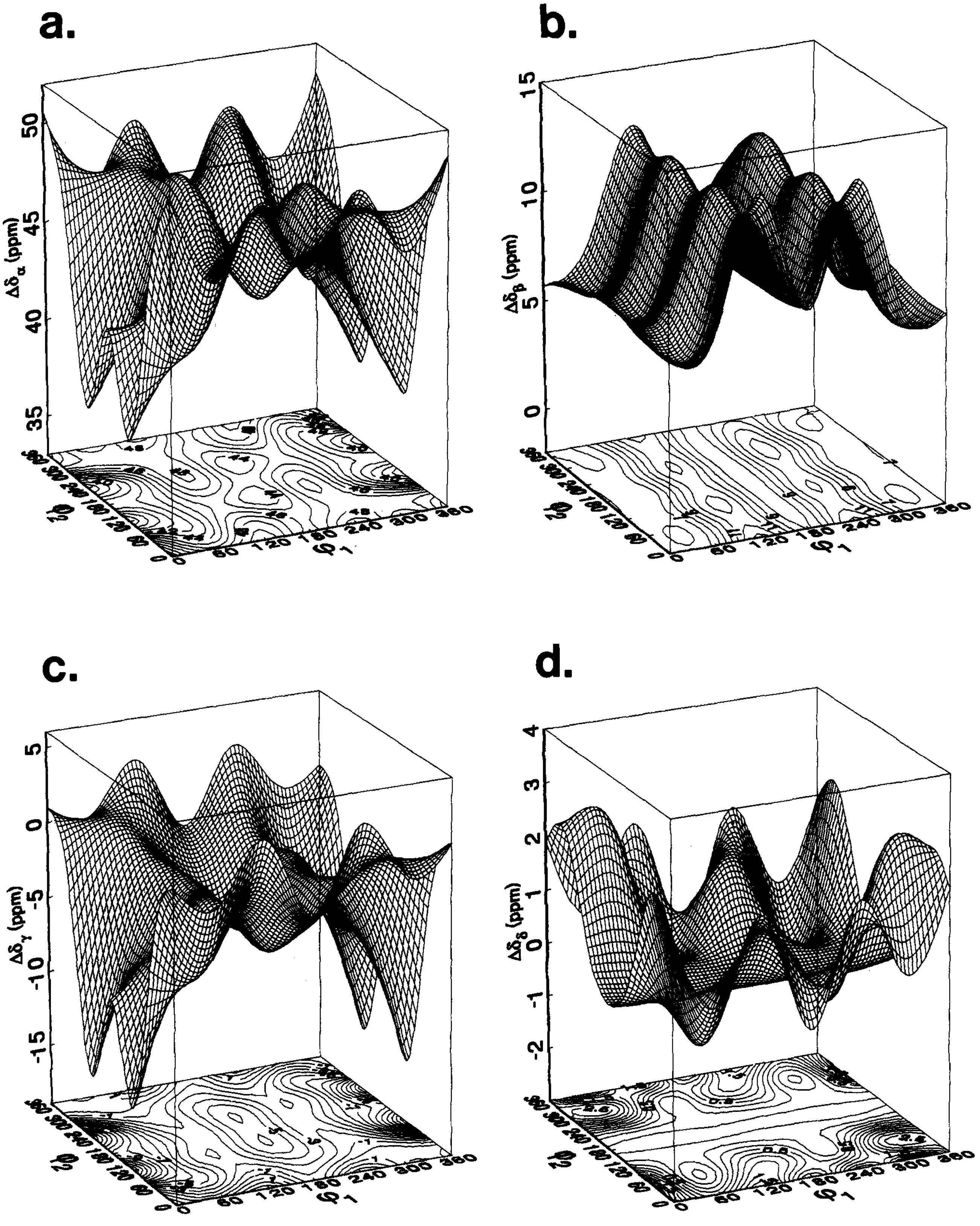

Figure 4. Calculated (IGLO Basis Set II′, HF/6-31G*) surface and contour plots of substituent effects $\Delta\delta_i$ in ppm for each of the carbons in 1-butanol (**4**) plotted as a function of the dihedral angles φ_1 and φ_2, measured about the C1−C2 and C2−C3 bonds, respectively: (a) $\Delta\delta_\alpha(\varphi_1,\varphi_2)$, the contour lines are separated by 1 ppm; (b) $\Delta\delta_\beta(\varphi_1,\varphi_2)$, the contour lines are separated by 0.5 ppm; (c) $\Delta\delta_\gamma(\varphi_1,\varphi_2)$, the contour lines are separated by 1 ppm; and (d) $\Delta\delta_\delta(\varphi_1,\varphi_2)$, the contour lines are separated by 0.25 ppm.

the four γ-substituents are given in Figures 2c−5c. Note the similarities in the ranges and shapes of the surfaces for a particular substituent. The usual *γ-gauche* and *γ-anti* values correspond to $\varphi_1 = 60°$ and 180°, respectively.[7] An unexpected feature of the IGLO results is the substantial dependence of *γ-gauche* effects on φ_2. In Table 2, for example, the calculated values −4.3, −3.7, −5.6, and −5.6 ppm for $-CH_3$, −CN, −OH, and −F, respectively, for g^+g^+ arrangements in Figure 1 are typical of *γ-gauche* effects. However, for *syn*-axial g^+g^- (and g^-g^+) arrangements the calculated *γ-gauche* effects are substantially more positive [$\Delta\delta_\gamma(g^+g^-) = 0.3, -0.2, 0.1, -0.7$ ppm]. The substituent dependencies of *γ-gauche* effects for

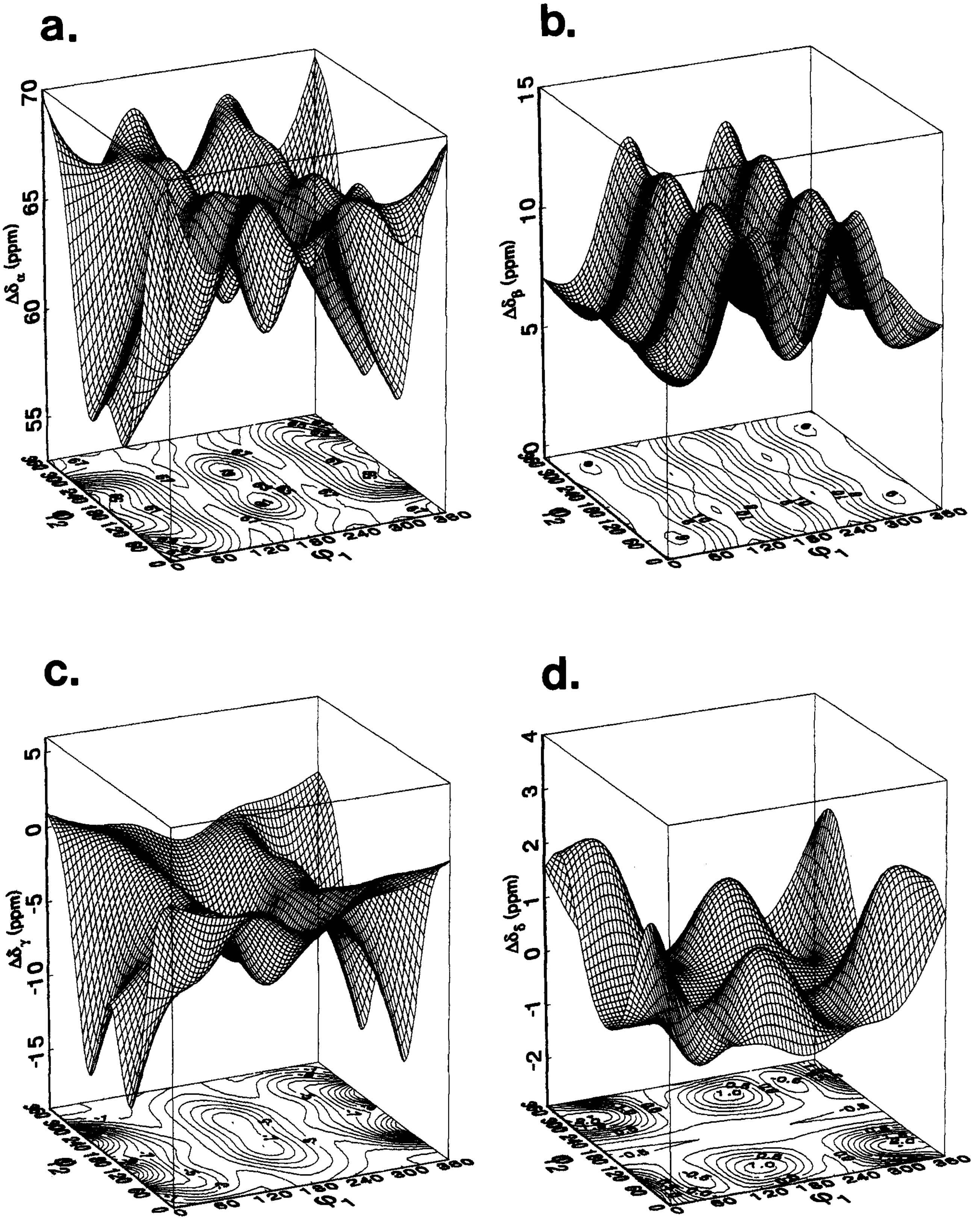

Figure 5. Calculated (IGLO Basis Set II′, HF/6-31G*) surface and contour plots of substituent effects $\Delta\delta_i$ in ppm for each of the carbons in 1-fluorobutane (**5**) plotted as a function of the dihedral angles φ_1 and φ_2, measured about the C1−C2 and C2−C3 bonds, respectively: (a) $\Delta\delta_\alpha(\varphi_1,\varphi_2)$, the contour lines are separated by 1 ppm; (b) $\Delta\delta_\beta(\varphi_1,\varphi_2)$, the contour lines are separated by 1 ppm; (c) $\Delta\delta_\gamma(\varphi_1,\varphi_2)$, the contour lines are separated by 1 ppm; and (d) $\Delta\delta_\delta(\varphi_1,\varphi_2)$, the contour lines are separated by 0.25 ppm.

g^+t arrangements should be similar to those in g^+g^+ arrangements.

Table 3 includes data designed to show the γ-effects of substituents for fixed geometries. The first two sets of data, which are close to g^+g^+ conformations, are qualitatively consistent with the predicted trend to more negative effects with increasing electronegativity. These trends are also followed for the g^+t and g^-t conformations in Table 3, but experimental data for γ-*gauche* effects in *syn*-axial (g^+g^-) arrangements appear not to be available for these molecules. In g^+g^- arrangements

Table 3. Comparison of Calculated α-, *β*-, *γ*-, and *δ*-Effects (6-31G*, BS II′) for a Series of 1-Substituted Butanes with Experimental Data from a Series of Substituted Bicyclic Compounds[a]

	dihedral angles[c]		$\Delta\delta_\alpha$		$\Delta\delta_\beta$		$\Delta\delta_\gamma$		$\Delta\delta_\delta$	
compd[b]	φ_1	φ_2	calcd	expt	calcd	expt	calcd	expt	calcd	expt
1-Me-TD	63	57	6.0	−9.8	5.6	7.8	−4.4	−4.8	−0.5	0.3
1-OH-TD			42.5	26.5	6.9	0.6	−5.4	−5.6	−0.6	−0.5
1-F-TD			62.2	49.5	6.8	3.3	−5.4	−4.8	−0.7	−0.5
2*n*-Me-BH	57	70	5.6	4.4	5.6	5.4	−4.7	−7.5	−0.5	0.6
2*n*-CN-BH			1.7	0.1	3.0	3.4	−3.7	−4.9	−0.5	−0.7
2*n*-OH-BH			41.8	43.3	6.6	6.2	−5.9	−9.6	−0.5	0.3
2-*eq*-Me-TD	60	180	6.6	3.4	8.3	6.0	−4.5	−3.8	0.1	−0.1
2-*eq*-OH-TD			43.0	40.3	6.7	6.7	−5.5	−5.2	−0.3	−0.5
1-Me-BO	172	10	8.3	3.4	8.8	7.3	0.2	0.7	0.4	0.7
1-CN-BO[d]			3.0	2.6	4.6	3.2	−0.7	−1.6	−0.2	−1.7
1-OH-BO			46.0	44.5	8.0	6.5	−1.3	−0.2	0.1	−0.1
1-F-BO			65.6	69.8	7.1	4.9	−2.4	1.1	−0.2	0.0
2*x*-Me-BH	167	70	8.8	6.8	8.7	6.7	−0.2	0.4	0.8	0.9
2*x*-CN-BH			2.6	1.0	4.6	5.5	−1.1	−1.5	0.0	−1.6
2*x*-OH-BH			45.9	45.1	8.4	7.9	−3.1	−5.2	1.2	−1.5
2*x*-F-BH			65.4	65.9	7.2	5.3	−3.9	−7.7	1.0	−2.0
2-*ax*-Me-TD	303	183	6.5	−1.3	5.9	2.8	−4.6	−2.8	0.2	0.4
2-*ax*-OH-TD			42.9	36.1	6.5	3.7	−5.7	−4.7	−0.3	−0.1

[a] Angles are in degrees and substituent effects are given in ppm. [b] Unless otherwise noted, data were obtained from ref 58. [c] These angles are contained in the spline interpolation tables. These were chosen to be within ca. 2.5° of the MMX results. [d] Della, E. W.; Gangodawila, H. *Aust. J. Chem.* **1989**, *42*, 1485−92.

of *trans*-decalols the observed *γ*-effects −0.2 and 1.4 ppm are consistent with the prediction of more positive values for φ_2 = 300°. Substituent effects have been reported for 1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones[56] with substituents $-CH_3$, $-OCH_3$, and −F at the 3-*exo* position. Because of the large number of substituents these are also not ideal molecules for comparison, but the experimental values at the C7 carbon [$\Delta\delta_\gamma(g^+g^-)$ = −0.09, −0.21, and −0.36 ppm, respectively] also support the prediction of substantially more positive values in g^+g^- arrangements.

The *γ-anti* effects[7,57] (φ_1 = 180°) are predicted to decrease substantially and monotonically in the series [$\Delta\delta_\gamma(tg^+)$ = −0.3, −1.2, −3.4, and −4.2 ppm]. This trends is consistent, for example, with those in 2-substituted adamantanes,[7] and with the experimental data in Table 3 for the 2-*exo*-substituted bicyclo[2.2.1]heptanes. The latter exhibit *γ*-effects which range from 0.4 to −7.7 ppm for the series of four substituents. In the 3-substituted 1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones,[56] substituents at the 3-*endo* position also correspond to arrangements close to tg^+. For the series of compounds having $-CH_3$, $-OCH_3$, and −F at the 3-*endo* position, the experimental values are −0.75, −3.87, and −4.14 ppm, respectively,[56] in qualitative conformity with the IGLO results.

4. *δ*-Effects. Entered in Table 2 and plotted in Figures 2d−5d are the calculated *δ*-substituent effects $\Delta\delta_\delta(\varphi_1,\varphi_2)$ for the 1-substituted butanes **2**−**5**. Not surprisingly, the ranges of the calculated *δ*-effects are only a few parts per million and the most pronounced features in the plots are the ca. 2 ppm maxima for the *syn*-axial (g^+g^- and g^-g^+) arrangements of **2**, **4**, and **5**. Maxima also occur in these conformations of pentanenitrile (**3**) but they are substantially reduced in magnitude. The next most prominent features in the surface and contour plots for **2**, **4**, and **5** are the minima of about −0.5 ppm for the g^+g^+ and g^-g^- conformations. In the next section it will be shown that the IGLO *δ*-effects reproduce these and most other conformational features in the experimental data for multicyclic compounds. Since the surface plot for *δ*-effects in pentanenitrile **3** (Figure 3d) is relatively flat, these conformational features would probably be difficult to detect. The small, relative maxima of about 0.7 ppm which occurs near φ_1, φ_2 = 135°, 60° (225°, 300°) become more pronounced in the series from $-CH_3$ to −F. Although these features arise from the interpolated data between φ_1 = 120 and 180°, it seems unlikely that these are artifacts of the interpolation. Unfortunately, these conformations do not occur for the molecules described in the next section.

Except for the 2-*exo*-substituted bicyclo[2.2.1]heptanes in Table 3 the agreement between calculated and experimental *δ*-effects is reasonable. Furthermore, in 3-substituted 1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones, substituents at the 3-*exo* position approximate g^+g^- geometries. The $-CH_3$, $-OCH_3$, and −F groups lead to $\Delta\delta_\delta$ values of 1.91, 1.34, and 1.05 ppm, respectively, at the *syn*-methyl carbons. These are in qualitative conformity with the predicted correlation with substituent electronegativity.

B. Comparison of Conformational Dependencies in Cyclic Molecules: Branching Effects. A major problem in studies of NMR substituent effects is one of sorting out the importance of conformational, substituent, and branching effects. The latter is known to be exceedingly important for the signs and magnitudes of substituent effects.[7] In the empirical formulation of eq 1 such effects are implicit in the term *S* which is called a *steric correction factor*. These can be as large as −15 ppm for highly branched carbon and bonded groups.[1−5] Since conformational dependencies of chemical shifts have not previously been elucidated with such great detail, it has not been possible to separate branching from conformational effects. However, a previous study of the conformational dependence of *γ*-effects[9] demonstrated that branching leads to substantial modifications of the torsion angle dependencies of the chemical shifts. To compare the calculated and experimental conformational dependencies it is necessary to find NMR data for suitable model compounds, e.g., "rigid" molecules with no additional heteroatoms, no additional branching at carbons C1−C5, and a unique set of dihedral angles associated with the linkage. Actual bicyclic molecules will differ in the extent of branching at some or all positions.

Since there are few ^{13}C NMR results for "rigid" compounds with nitrile and fluoro groups, detailed comparisons of calculated

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Table 4. Comparison of Calculated α-, β-, γ-, and δ-Effects (6-31G*, BS II′) for Pentane with Experimental Data from a Series of "Rigid" Dimethylbicyclo Compounds[a]

	dihedral angles[c]		$\Delta\delta_\alpha$		$\Delta\delta_\beta$		$\Delta\delta_\gamma$		$\Delta\delta_\delta$	
compd[b]	φ_1	φ_2	calcd	expt[d]	calcd	expt[d]	calcd	expt[d]	calcd	expt[d]
2-*ax*,10-*eq*-DMTD	57	70	5.6	2.8^{STT}	5.6	5.7^{TTT}	−4.7	-4.7^{TTP}	−0.5	-0.8^{TP}
2-*ax*,10-*eq*-DMTD	70	57	6.7	-2.2^{STT}	6.4	2.5^{TTT}	−3.8	-3.4^{TTP}	−0.5	-0.6^{TP}
2-*ax*,4-*eq*-DMTD	73	180	7.2	0.5^{STS}	6.9	7.8^{TST}	−3.6	-6.6^{STP}	0.1	0.2^{TP}
2-*eq*,4-*ax*-DMTD	73	180	7.2	1.7^{STS}	6.9	5.6^{TST}	−3.6	-6.4^{STP}	0.1	0.2^{TP}
1,3-*endo*-DMBH	130	161	9.2	4.7^{PTS}	9.4	9.1^{TSQ}	−0.6	1.6^{SQP}	−0.1	1.0^{QP}
1,3-*endo*-DMBH	161	130	9.0	7.6^{PQS}	8.9	7.4^{QST}	−0.9	1.9^{STP}	0.1	0.8^{TP}
1,3-*exo*-DMBH	163	234	9.1	8.0^{PQS}	8.9	7.7^{QST}	−0.8	1.9^{STP}	0.3	0.5^{TP}
2-*eq*,4-*ax*-DMTD	180	73	8.6	3.3^{TTS}	8.4	9.9^{TST}	−0.5	-0.3^{STP}	0.5	0.7^{TP}
2-*ax*,4-*eq*-DMTD	180	73	8.6	5.6^{TTS}	8.4	8.8^{TST}	−0.5	-0.5^{STP}	0.5	0.7^{TP}
1,4-DMBH	180	180	8.6	7.5^{PQS}	8.3	7.2^{QSQ}	−1.1	1.6^{SQP}	0.0	1.0^{QP}
2-*eq*,4-*eq*-DMTD	180	180	8.6	5.9^{STS}	8.3	8.8^{TST}	−1.1	-0.4^{STP}	0.0	0.0^{TP}
2-*eq*,4-*eq*-DMTD	180	180	8.6	3.4^{STS}	8.3	9.7^{TST}	−1.1	-0.6^{STP}	0.0	0.0^{TP}
1,M3-DMBO	190	219	8.8	3.6^{PQS}	8.6	7.5^{QST}	−1.0	0.8^{STP}	0.1	0.0^{TP}
1,M3-DMBO	219	190	9.1	4.5^{TTS}	9.2	10.0^{TSQ}	−0.7	1.6^{SQP}	0.0	0.0^{QP}
1,3-*exo*-DMBH	234	163	9.3	7.1^{PTS}	9.4	10.8^{TSQ}	−0.7	1.2^{SQP}	0.2	0.5^{QP}

[a] Angles are in degrees and substituent effects are given in ppm. [b] All data taken from refs 15−19 or the compilation of Whitesell and Minton.[58] [c] These angles are contained in the spline interpolation tables. These were chosen to be within 2.5° of the PCMODEL MMX results. [d] The superscripts *ijk* (where *i*, *j*, *k* = primary, secondary, tertiary, and quaternary) denote the branching patterns at the carbon atom of interest *j* and the attached carbons *i* and *k*. For methyl groups in the last column there is only one attached group.

data and experimental results in this section are restricted to those for methyl- and hydroxy-substituted compounds. Compounds of suitable rigidity and for which ^{13}C chemical shift data are available[56] include mono- and disubstituted *trans*-decalins (TD), bicyclo[2.2.1]heptanes (BH), and bicyclo[2.2.2]-octanes (BO). Even in the most favorable cases branching at the C2−C4 carbons may be greater than in the model compounds. The best agreement is expected for those cases in which the branching is closest to those in the model compounds, e.g., primary carbons for δ-effects. Because of the emphasis on δ-effects, data in Table 4 are restricted to molecules with methyl groups at the Cδ positions. These include several dimethyl-*trans*-decalins (DMTD) having butane moieties near the conformations depicted in Figure 1. For the Cα−Cγ carbons it was also of interest to compare the experimental results with the predicted torsion angle dependencies. Dihedral angles φ_1 and φ_2 for each moiety are entered in the second and third columns. These are the estimated angles which occur in the 5° spline interpolations[51] of the calculated IGLO results. These angles differ by no more than ca. 2.5° from the values inferred from molecular mechanics calculations.[52,53] The substituent-induced shifts from the pentane/butane data are given for these angles. The experimental data for dimethylbicyclo[2.2.1]-heptanes (DMBH) and dimethylbicyclo[2.2.2]octanes (DMBO) correspond to sets of dihedral angles which are substantially different from those in Figure 1.

Since the experimental chemical shift data for bicyclo[2.2.1]-heptanols, *trans*-decalols, and steroids have been used extensively for investigating the structural and stereochemical aspects of δ-effects, it seemed appropriate to include detailed comparisons with a wider class of molecules covering a larger range of conformations. The restriction of the Cδ carbon to methyl groups was removed. Table 5 includes calculated and experimental α-, β-, γ-, and δ-effects for bicyclic molecules covering a range of dihedral angles. This is actually a more manageable subset (23 items) of the larger set (45 items) included in the supplementary material. The subset was restricted to include only those items in which the Cδ carbon is primary or secondary and the four cases in which the C_γ carbon is secondary with secondary attached groups (*SSS*), but it is representative of all conformations in the larger set. It includes arrangements approximating all nine of those in Figure 1 and all distinctly different ones. Included for each entry in the table are the estimated dihedral angles φ_1 and φ_2. In the 5° spline interpolation tables for the calculated $\Delta\delta_i$, these angles are closest to those inferred from molecular mechanics calculations.[53]

All *experimental data* in Tables 4 and 5 include three-letter codes *ijk* as superscripts to indicate the branching (*i*, *j*, *k* = primary, secondary, tertiary, or quaternary) at the carbon of interest *j* and attached groups *i* and *k*. For the 1-substituted butanes the Cα−Cδ carbons are designated *PSS, SSS, SSP, and SP*, respectively, branching situations which do not occur for the experimental data in Table 4. Thus, all examples in the tables reflect the importance of branching superimposed on conformational effects.

1. α-Effects. The calculated α-effect data $\Delta\delta_\alpha(\varphi_1,\varphi_2)$ in Tables 4 and 5 appear not to reproduce *conformational features* which might be implicit in the experimental data. The calculated −OH α-effects in Table 5 range from 42.3 to 47.9 ppm while the experimental ones range from 26.5 to 54.3 ppm. These results clearly show the implications on the calculated results of neglecting branching. The disparities between the calculated and experimental results parallel the extent of branching at the α- and the two β-carbons, e.g., the largest standard deviation 15.9 ppm occurs for the two entries in which the α-carbon is quaternary. Since all of the remaining entries have tertiary α-carbons, it is necessary to examine the importance of branching at the β-carbons. The standard deviations between calculated and experimental results for α-effects at tertiary carbons having quaternary and secondary β-carbons, tertiary and secondary β-carbons, and only secondary β-carbons are 8.6, 4.4, and 2.2 ppm, respectively. Thus, even in the best cases the conformational predictions for α-effects are not well correlated with the experimental results. In part, this must reflect α-carbons which are tertiary or quaternary. Possibly, an even more important factor leading to substantial disparities is the dependence on more than two dihedral angles. For example, α-effects of a substituent X at the C4 position of heptane will depend on the four dihedral angles about C1−C2, C3−C4, C4−C5, and C5−C6 bonds.

2. β-Effects. All but the first two $\Delta\delta_\beta$ entries for dimethylbicyclic compounds in Table 4 have secondary β-carbons. If these two are excluded, the standard deviation between calculated and experimental results for the remaining entries is 1.1 ppm, a smaller disparity than for α-substituents. Comparable agreement is noted in Table 5 for the nine −OH β-effect entries with secondary Cβ carbons. The surface plots of $\Delta\delta_\beta$ in Figure 2a and 2d suggest an independence on φ_2 and a dependence on

Table 5. Comparison of Calculated α-, β-, γ-, and δ-Effects (6-31G*, BS II′) for 1-Butanol with Experimental Data from a Series of "Rigid" Bicyclic Alcohols[a]

	dihedral angles[c]		$\Delta\delta_\alpha$		$\Delta\delta_\beta$		$\Delta\delta_\gamma$		$\Delta\delta_\delta$	
compd[b]	φ_1	φ_2	calcd	expt[d]	calcd	expt[d]	calcd	expt[d]	calcd	expt[d]
1-OH-TD	57	57	42.3	26.5^{SQT}	6.5	0.6^{QTS}	−5.6	-5.6^{TSS}	−0.5	-0.5^{SSS}
1-OH-TD	68	57	42.8	26.5^{TQS}	7.4	5.6^{QSS}	−5.1	-5.2^{SSS}	−0.5	-0.5^{SSS}
1-Me,2-*eq*-OH-TD	68	172	43.6	37.5^{STQ}	7.4	5.3^{TQS}	−4.8	-4.8^{QSS}	−0.3	-0.4^{SSS}
2-*eq*-OH-TD	60	180	43.0	40.3^{STT}	6.7	6.7^{TTS}	−5.5	-5.2^{TSS}	−0.3	-0.5^{SSS}
2-*eq*-OH,6-Me-TD	57	188	42.7	40.7^{STT}	6.5	6.6^{TTS}	−5.8	-6.3^{TSS}	−0.3	-0.5^{SSS}
2*n*-OH,6*x*-Me-BH	55	196	42.4	42.8^{STT}	6.5	6.2^{TTT}	−6.0	-11.1^{TTP}	−0.3	-0.5^{TP}
2-*ax*-OH,6-Me-TD	70	292	47.2	42.5^{STT}	7.6	2.7^{TTQ}	−0.2	-0.2^{TQP}	1.9	3.4^{QP}
2*n*-OH,6*n*-Me-BH	55	297	47.0	54.3^{STT}	6.3	5.3^{TTT}	−0.2	1.4^{TTP}	2.5	2.0^{TP}
2*x*-OH,7*a*-Me-BH	84	177	45.0	48.2^{STT}	8.9	7.5^{TTT}	−3.6	-4.7^{TTP}	−0.3	-0.8^{TP}
2*n*-OH,4-Me-BH	125	159	46.2	42.0^{TTS}	11.6	9.3^{TSQ}	−2.5	0.9^{SQP}	−0.2	0.6^{QP}
1-Me,3-*eq*-OH-TD	180	68	45.3	44.8^{STS}	7.5	8.8^{TSQ}	−3.8	0.8^{TQP}	0.9	0.9^{QP}
2x-OH,6x-Me-BH	175	198	44.3	44.6^{STT}	7.4	8.1^{TTT}	−5.9	-5.1^{TTP}	−0.2	-0.9^{TP}
2*x*-OH,6*n*-Me-BH	175	303	45.6	46.9^{STT}	7.6	7.7^{TTT}	−3.4	-2.5^{TTP}	0.7	-0.5^{TP}
1-Me,2-*eq*-OH-TD	177	303	45.6	37.5^{QTS}	7.5	8.3^{TSS}	−3.3	-2.8^{SSS}	0.8	-1.2^{SST}
2-*eq*-OH,6-Me-TD	180	287	44.1	40.7^{STT}	7.5	6.6^{TTQ}	−4.0	0.9^{TQP}	0.8	1.1^{QP}
2*x*-OH,4-Me-BH	240	162	47.9	44.7^{TTS}	11.6	12.3^{TSQ}	−2.2	0.3^{SQP}	−0.3	-0.5^{QP}
1-Me,3-*ax*-OH-TD	287	73	47.0	45.5^{STS}	8.0	5.7^{TSQ}	−0.6	-0.4^{SQP}	1.7	2.2^{QP}
2-*ax*-OH,6-Me-TD	300	190	43.1	42.5^{STT}	6.8	2.7^{TTS}	−5.4	-3.3^{TSS}	−0.3	0.1^{SSS}
2-*ax*-OH-TD	303	183	42.9	36.1^{STT}	6.5	3.7^{TTS}	−5.7	-4.7^{TSS}	−0.3	-0.1^{SSS}
1-Me,2-*ax*-OH-TD	310	175	42.4	33.3^{STQ}	6.2	4.4^{TQS}	−6.3	-7.2^{QSS}	−0.3	-0.2^{SSS}
2-*ax*-OH,6-Me-TD	282	308	44.0	42.5^{TTS}	8.4	6.9^{TSS}	−3.8	-5.2^{SSS}	−0.3	1.6^{SSQ}
1-Me,2-*ax*-OH-TD	290	308	43.3	33.3^{QTS}	7.6	6.5^{TSS}	−4.4	-6.7^{SSS}	−0.4	-0.4^{SST}
2-*ax*-OH-TD	292	303	42.8	36.1^{TTS}	7.4	7.4^{TSS}	−5.0	-6.9^{SSS}	−0.5	-0.5^{SST}

[a] Angles are in degrees and substituent effects are given in ppm. [b] All data taken from ref 58. In this abbreviated notation *n*, *x*, and *a* denote *endo*, *exo*, and *anti*, respectively. [c] These angles are contained in the spline interpolation tables. These were chosen to be within ca. 2.5° of the PCMODEL MMX results. [d] See footnote *d* of Table 4.

φ_1 which monotonically increases from about 6 ppm for small dihedral angles reaches a maximum near 10 ppm at 120°, and then shows a slight dip and another maximum at 240°. The experimental data in Tables 4 and 5 are qualitatively consistent with these predictions. Unfortunately, in Table 5 the entries between 125 and 240° only cover a narrow (13°) range around $\varphi_1 = 180°$.

3. γ-Effects. The agreement between the calculated and experimental γ-effects in Tables 4 and 5 is fairly good if those entries for *quaternary* Cγ carbons are eliminated. It is even better for the small set of entries in Table 5 for which tertiary carbons are also eliminated. Further elimination of those entries in Table 5 in which the γ-carbon is bonded to quaternary carbons reduces the standard deviation between the calculated and experimental data to 1.3 ppm. This subset (*SSS*, *TSS*, and *SST*) includes g^+g^+ and g^-g^- arrangements for which the calculated value of −5.6 ppm is in reasonable accord with experimental values in the range −5 to −7 ppm. It also includes tg^- conformations for which the calculated value of −3.3 ppm is consistent with the experimental value of −2.8 ppm. Missing from *this subset* in Table 5 are examples of the *syn*-axial (g^+g^-) conformations. It is necessary to examine the subset in which the γ-carbon is tertiary and not bonded to quaternary carbons (*STS*, *TTS*, *TTP*) for which the standard deviation is 2.5 ppm. This set includes both g^+g^+ and g^+g^- arrangements with experimental values of −8.1 and 1.4 ppm compared to the 1-butanol values of −5.0 and −0.2 ppm, respectively. The only other experimental entry for a g^+g^- (*TQP*) arrangement in Table 5 is −0.2 ppm, a value in fortuitously exact agreement with the calculated value. The g^+g^- conformation is not represented by the data in Table 4.

The calculated values in Tables 4 and 5 correspond to molecular arrangements having only γ-effects of negative sign. Branching effects can change the sign of these effects. In the γ-effect model based on 2,3-dimethylbutane/2-methylbutane, for example, the calculated γ-effects are positive in sign for dihedral angles in the range 120−240°.[9] Although the latter model is not entirely appropriate for the bicyclic molecules represented in Table 4, it is interesting to note that all four $\Delta\delta_\gamma$ with $\varphi_1 < 120°$ in Table 4 are negative, and of the remaining eleven entries having dihedral angles in the range 120−140°, seven are positive in sign.

4. δ-Effects. The bicyclic molecules in Table 4 were limited to those in which the Cδ carbon is a methyl group. The calculated values for δ-effects cover only the narrow range from −0.5 to +0.5 ppm but there is good agreement between calculated and experimental results for the g^+g^+, g^+t, tg^+, and *tt* conformations. The standard deviation is 0.8 ppm between calculated and experimental results for the four situations in which methyl groups are attached to quaternary carbons. For the remaining eleven entries (*TP*) the standard deviation is only 0.3 ppm. Conspicuously missing from the $-CH_3$ δ-effect experimental data sets in Table 4 are values for the *syn*-axial (g^+g^- and g^-g^+) arrangements.

In Table 5 only 11 of the 23 entries apply to situations in which the Cδ carbons are methyl groups. The standard deviation between the calculated and experimental results among this set is 0.5 ppm. Not surprisingly, the largest disparities occur in those situations in which the δ-carbon is flanked by quaternary or tertiary carbons. The smallest discrepancies (the standard deviation is 0.2 ppm for the eight entries) occur in those cases in which the carbons attached to the δ-carbon are both secondary.

In general, the agreement for conformational dependencies of −OH δ-effects in Table 5 is satisfactory. For g^+g^+ and g^-g^- arrangements, the calculated value of ca. −0.5 ppm agrees with most of the experimental values. Predicted values of about −0.3 ppm for the g^+t entries are also in comparable agreement. Calculated substituent shifts of ca. 2 ppm in g^+g^- arrangements are consistent with the experimental values in the range 2−3 ppm. Only two of the entries in Table 5 conform to these conformations but other examples are known.[20−29] Unfortunately, the simple 1-butanol/butane model for δ-effects fails on comparing the data for the tg^+ and tg^- arrangements. With the exception of the cases in which the Cδ carbon is *primary attached to quaternary*, calculated values have signs opposite to the experimentally inferred ones. Near *tt* arrangements the predicted deshielding by 0.3 ppm is in the right direction, but it is only about a third of the experimental substituent shifts.

V. Local Bond Contributions

In order to gain some insight into the conformational dependencies of the δ-effects, contributions of the individual localized MO's to the total shieldings at the Cγ and Cδ carbons in compounds **1**−**5** were examined as a function of the two torsion angles. The major diamagnetic (positive) contribution to the isotropic ^{13}C shielding is 200.9 ppm from the inner shell 1s orbitals. This number is the same (±0.1 ppm) for all of the carbon atoms in these compounds independent of the molecular conformation and substituent. Negative (deshielding) contributions arise from localized MO's associated with C−C and C−H bonds. The local bond contributions LBC's represent the sum of local paramagnetic and diamagnetic contributions to the localized MO's. To show the importance of the localized bond contributions to the *substituent* effects, the changes Δ_{LBC} from the corresponding butane LBC's were examined for each of the four bonds at the γ- and δ-carbons. Analyses of the local bond contributions for the 1-butanol γ-effects indicate that the most important contributions, including those associated with asymmetry about $\varphi_1 = 180°$, arise from the C2−C3 local bond contributions. As a consequence, the surface and contour plots for Δ_{LBC}(C2−C3) in 1-butanol are very similar to those for the $\Delta\delta_\gamma$ in Figure 4c. The importance of the LBC contributions in this situation is in marked contrast with that for γ-effects in butane in which important contributions also occur for the C−H bond pointing away from the γ-methyl.[8]

For all four substituents in Table 2 the calculated δ-effects assume their maximum values (2.6, 0.7, 2.4, and 2.0 ppm for X = $-CH_3$, −CN, −OH, and −F, respectively) in *syn*-axial arrangements ($\varphi_1 = 60°$, $\varphi_2 = 300°$). Since these have been ascribed to steric effects associated with the substituent and the proximate C−H bonds at the Cδ carbon it may be instructive to examine the crowding in the various structures. The HF/6-31G* geometries for *syn*-axial arrangements for **2**−**5** are depicted in Figure 6a−d. In all cases the orientations of the terminal methyl group are similar and one of the bonds, e.g., the C4−H6 bond in 1-butanol, is in closest proximity to the substituent. The structural changes in Figure 6 show no obvious correlations with the magnitudes of the δ-effects. In all cases the Cδ−H6 bond is compressed by about 0.005 Å in comparison with the Cδ−H7 and Cδ−H8 bonds. Based on the internal Cα−Cβ−Cγ angles in Figure 6, it appears that crowding is greatest for the pentane and decreases monotonically in the series. Here, the smaller magnitude of the δ-effect associated with the nitrile group may be associated with the absence of either bond pairs or lone pairs in the sterically crowded region.

Since the analyses of the local bond contributions are qualitatively the same for all four substituents, only the 1-butanol results will be described here. For the C4 carbon of 1-butanol the changes Δ_{LBC} in the local bond contributions associated with each of the four bonds are plotted in Figure 7a−d as functions of the two dihedral angles. For g^+g^- and g^-g^+ arrangements the most obvious features are the relative maxima for the C4−H6 and C4−H8 bonds in Figure 7, plots a and c, respectively. Note that the LBC's for the C4−H7 bond also make substantial contributions to the δ-effects in *syn*-axial arrangements even though this bond is pointing away from the −OH group. In the g^+g^- arrangement depicted in Figure 6c the C4−H6 bond distance is compressed (1.080 Å) in comparison to C4−H7 and C4−H8. Since the C4−H7 bond also has significant Δ_{LBC} in g^+g^- arrangements, shortening of the C4−H6 bond is probably not responsible for the substantial ca. 2 ppm deshielding. Moreover, shielding calculations for pentane and butane at the Basis Set II′ level with a standard geometrical model (e.g., tetrahedral angles and all r_{CH} = 1.084 Å) lead to an 18.3 ppm calculated δ-effect $\Delta\delta_\delta(60°,300°)$. In this more crowded situation comparable LBC's occur for the C5−H6 and C5−H7 bonds even though the bond lengths are identical.

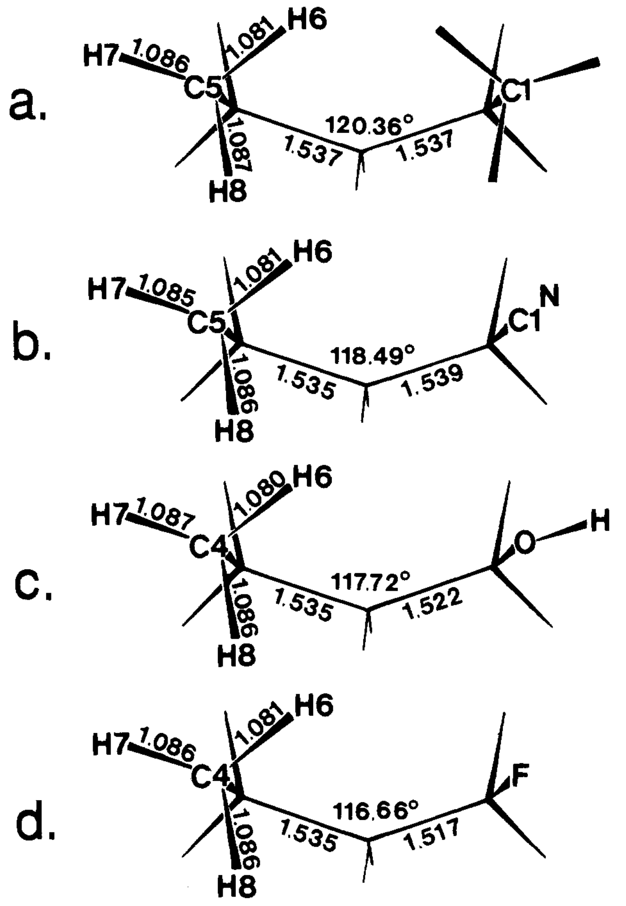

Figure 6. Bond orientations and internuclear separations in (HF/6-31G*) in *syn*-axial arrangements ($\varphi_1 = 60°$, $\varphi_2 = 300°$) of (a) pentane (**2**) for which *r*(C1−C5) = 3.247 Å, *r*(C1−H6) = 2.827 Å, (b) pentanenitrile having *r*(C1−C5) = 3.129 Å, *r*(C1−H6) = 2.653 Å, (c) 1-butanol with *r*(O−C4) = 2.948 Å, *r*(O−H6) = 2.460 Å, and (d) 1-fluorobutane with *r*(E−C4) = 2.910 Å, *r*(F−H6) = 2.404 Å.

VI. Conclusions

Ab initio MO calculations here performed at the HF/6-31G* and IGLO Basis Set II′ level provide a satisfactory description of ^{13}C chemical shifts and α-, β-, γ-, and δ-effects for 1-substituted butanes with $-CH_3$, −CN, −OH, and −F substituents at the C1 positions. Averaging the ^{13}C chemical shifts over the two torsional barriers slightly improves the agreement between calculated and experimental values.

The isotropic ^{13}C chemical shifts for the substituted butanes were examined as functions of the dihedral angles φ_1 and φ_2 about the C1−C2 and C2−C3 bonds, respectively. For each of the α-, β-, γ-, and δ-effects there are substantial similarities in the surface and contour plots for all four substituents. This suggests that the *conformational* dependencies are primarily determined by the carbon position, while the surface elevations (or torsion averaged values $\langle\delta_i\rangle$) depend on the nature of the substituent, e.g., electronegativity.

In contrast to β-effects which are almost independent of φ_2, the calculated α-, γ-, and δ-effects show substantial variations

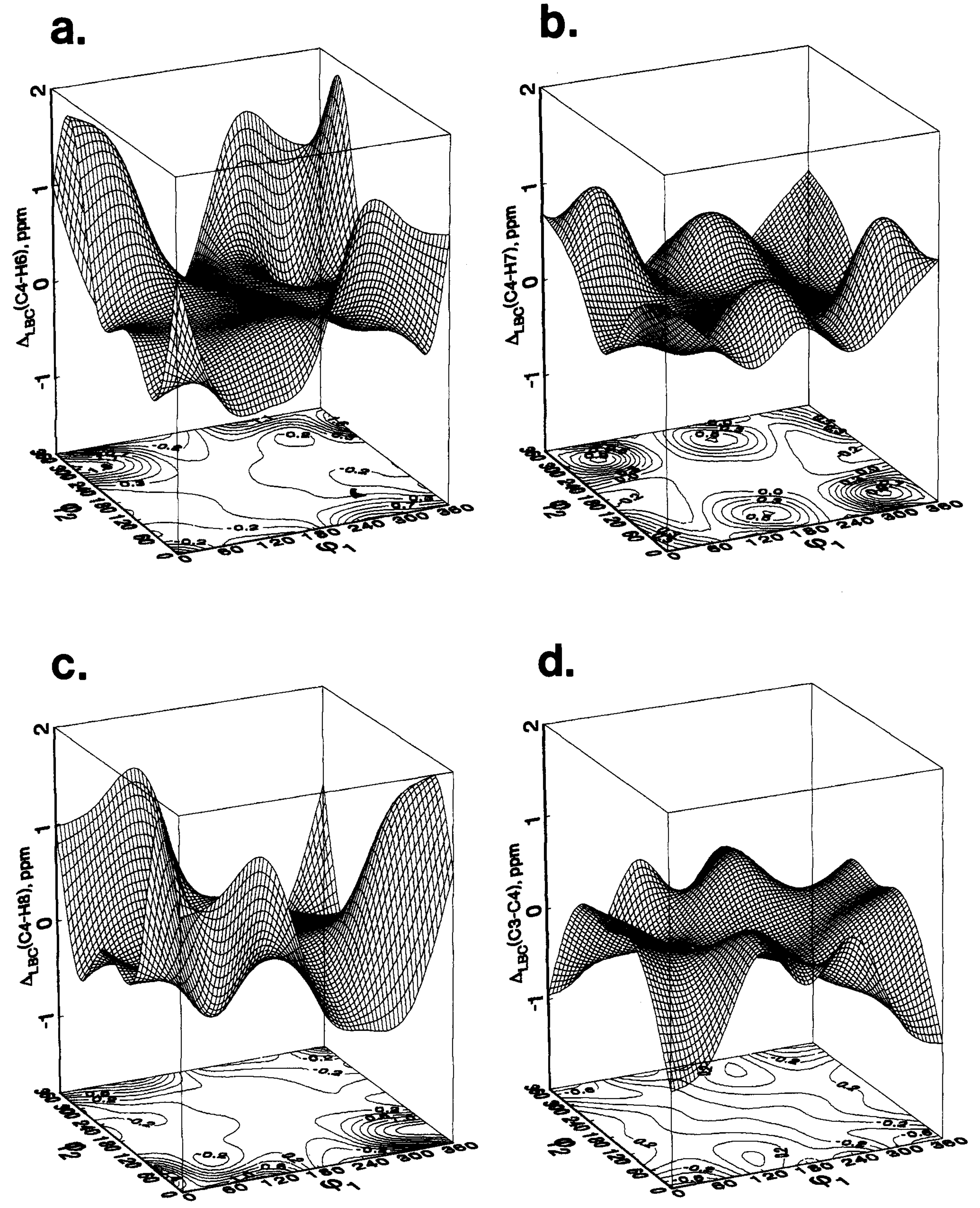

Figure 7. Calculated (IGLO Basis Set II′, HF/6-31G*) surface and contour plots of the local bond contributions Δ_{LBC} in ppm for each of the bonds at the δ-carbon atom plotted as a function of the dihedral angles φ_1 and φ_2: (a) the C4−H6 bond, the contour lines are separated by 0.25 ppm; (b) the C4−H7 bond, the contour lines are separated by 0.1 ppm; (c) the C4−H8 bond, the contour lines are separated by 0.2 ppm; and (d) the C3−C4 bond, the contour lines are separated by 0.2 ppm.

with both dihedral angles. The calculated angularly dependent results for the 1-substituted butanes are compared with experimental data for several series of substituted bicyclo[2.2.1]heptanes, bicyclo[2.2.2]octanes, and *trans*-decalins. The rigidity in these molecules arises from more extensive branching than in the model compounds. Even though branching along the carbon chain modifies the conformational dependencies, a number of useful correlations between calculated and experimental data emerge. The substantial substituent dependence of the chemical shift at the Cα carbon is predicted, but other factors obscure the conformational dependencies. It seems likely that the situation at the Cα carbon of *cyclic* molecules is more complicated because at least two sets of dihedral angles are involved. The experimental data for β-effects are consistent with the predicted dependence on φ_1 and independence of φ_2. The predicted dependencies of γ- and δ-effects on φ_1 and φ_2 are clearly seen in the experimental data which show substantially more positive values for g^+g^- than for g^+g^+ and g^+t arrangements. Most of the predicted conformational features of δ-effects clearly reproduce the salient features of the experimental data, including 2−3 ppm deshielding effects in *syn*-axial (g^+g^-) arrangements, small negative effects for g^+g^+ arrangements, and very small values for the all *trans* arrangements.

The IGLO C−H and C−C local bond contributions for the γ- and δ-carbon of each of the molecules were examined to explore the electronic features associated with the substituent effects. It is rather surprising that conformational features of γ-effects are dominated by the local bond contributions associated with the C2−C3 bond. At the Cδ carbon the maximum values for the C−H LBC's arise in the *syn*-axial arrangements in which the substituent closely approaches the C4−H6 or C4−H8 bond. For pentane (1-butanol) the angular dependence of the calculated δ-effects at the C5 (C4) carbons is dominated by the changes at the C5−H6 (C4−H6) or C5−H7 (C4−H8) bonds when they are close to the C1 methyl (OH) group.

Although chemical shifts are extremely sensitive to the stereochemical environment, the promise of their use in conformational analyses has been elusive. It seems likely that the recognition here of the importance of these additional conformational factors will be helpful in realizing this goal.

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Supplementary Material Available: All of the calculated Basis Set II′ chemical shifts and comparisons of calculated 1-butanol results with experimental data are given in two tables (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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