

# Computed $^{13}\text{C}$ NMR Chemical Shifts via Empirically Scaled GIAO Shieldings and Molecular Mechanics Geometries. Conformation and Configuration from $^{13}\text{C}$ Shifts

David A. Forsyth\* and Albert B. Sebag

Contribution from the Department of Chemistry, Northeastern University, Boston, Massachusetts 02115

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**Abstract:** Accurate (rms error  $\sim 3$  ppm) predictions of  $^{13}\text{C}$  chemical shifts are achieved for many of the common structural types of organic molecules through empirical scaling of shieldings calculated from gauge including atomic orbitals (GIAO) theory with a small basis set and with geometries obtained from computationally inexpensive molecular mechanics methods. Earlier GIAO calculations are shown to be much better at predicting relative chemical shifts when density functional theory with the B3LYP hybrid functional is used to account for electron correlation, in comparison with Hartree–Fock calculations. The GIAO isotropic shieldings need to be empirically scaled to achieve good numerical agreement with experimental  $\delta_{\text{C}}$ . GIAO calculations with different small basis sets are compared for a set of 38 model compounds containing C, H, O, and N with MMX and MM3 force fields and B3LYP/6-31G\* optimizations providing the geometries. The best MM3-based results are obtained with B3LYP/3-21G(X,6-31+G\*)/MM3 calculations in which the 3-21G basis set is augmented for heteroatoms with polarization and diffuse functions. The examples of the (*E*)- and (*Z*)-2-butenes, axial and equatorial methylcyclohexanes, *exo*- and *endo*-2-norbornanols, vulgarin and epivulgarin, and chair and twist-boat forms of  $3\alpha$ -hydroxy- $2\beta$ -(4-morpholinyl)- $5\alpha$ *H*-androstan-17-one are examined to establish whether  $\delta_{\text{pred}}$  values could determine the structure if only one of each pair of structures were available to provide experimental  $\delta_{\text{C}}$  values. The  $\delta_{\text{pred}}$  from B3LYP/3-21G(X,6-31+G\*)/MM3 calculations are adequate for addressing questions of conformation and relative stereochemistry.

Accurate prediction of  $^{13}\text{C}$  chemical shifts could become a tool that strongly complements if not rivals  $^1\text{H}$ – $^1\text{H}$  coupling constants,  $^1\text{H}$ – $^1\text{H}$  NOE measurements, and empirical chemical shift correlations for determination of conformations and configurations of organic molecules.  $^{13}\text{C}$  chemical shifts reflect structural features in a highly sensitive manner, but at present, most  $^{13}\text{C}$  chemical shift data that are reported are not used in a detailed analysis of structure. Schleyer, Gauss, and co-workers<sup>1</sup> have suggested that the combination of high-level ab initio optimized geometries, theoretically computed NMR chemical shifts, and experimental NMR data provides a tool that can be routinely applied for structural elucidation and characterization of new compounds. Practical applications so far are most extensive in the areas of carbocations and boron compounds, where high-level ab initio methods including electron correlation are necessary to properly describe structure and bonding.<sup>1–3</sup> Other studies oriented toward structure determination include an analysis of  $\text{C}_{84}$  fullerenes<sup>4</sup> and studies relating to the conformation of the rhodopsin chromophore.<sup>5</sup> Several studies

have explored the challenging problem of predicting  $^{13}\text{C}$  shifts in amides and peptides.<sup>6</sup>

Applications of theoretically computed  $^{13}\text{C}$  chemical shifts to organic structure determination have not yet become routine, despite the apparent capability to predict shifts of  $^{13}\text{C}$  and other nuclei at a sufficient level of accuracy to allow practical applications. To achieve the goal of routine practical use, *predicted  $^{13}\text{C}$  chemical shifts need to be accurate to within a very few ppm for molecules in solution that include a wide variety of functional groups and conformational characteristics. The predictions also need to be achieved at modest computational cost.*

There have been some discouraging signs despite the great promise and demonstrated successes of the various quantum mechanical methods for predicting chemical shifts. Several methods used with ab initio calculations are now available for calculating nuclear shieldings, such as the GIAO (gauge including atomic orbitals),<sup>7</sup> IGLO (individual gauge for localized orbitals),<sup>3,8</sup> CSGT (continuous set of gauge transformations),<sup>9</sup>

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and LORG (localized orbitals, local origin)<sup>10</sup> methods. The need for accurate geometries has been emphasized repeatedly, leading to the practice of performing geometry optimizations at high levels of ab initio theory, often with electron correlation included.<sup>1–3,12</sup> Such an approach can be quite expensive computationally, especially since many candidate structures for an organic molecule of even modest size can often be identified through simple consideration of possible conformations or through a systematic conformational search.

Recent studies also show that electron correlation contributions should be included to obtain the most accurate shielding tensors.<sup>13</sup> For example, significant improvements in chemical shift predictions can be achieved over Hartree–Fock SCF calculations through the use of the GIAO MP2 method.<sup>1</sup> Density functional theory (DFT) provides a lower cost alternative to the more traditional electron correlation techniques such as the Moeller–Ploesset (MP $n$ ) methods.<sup>14</sup> However, a recent comparison by Cheeseman, Trucks, Keith, and Frisch of models for calculating NMR shielding tensors found that, for GIAO calculations, the root-mean-square (rms) error in calculated <sup>13</sup>C shifts for a set of small molecules was 11.1 ppm at the Hartree–Fock 6-31G\* level and 12.5 ppm with a DFT method, the B3LYP hybrid functional.<sup>15</sup> Unfortunately, errors at >10 ppm are not very attractive to chemists for most practical applications, as discussed below. In their study, geometries for the set of model compounds were optimized at the B3LYP/6-31G\* level. The DFT GIAO predictions did improve to an rms error of 4.2 ppm with the large B3LYP/6-311+G(2d,p)/B3LYP/6-31G\* basis set while the HF GIAO predictions with the same basis set remained at the same large size of rms error. Apparently based on this study, the user's reference for the Gaussian 94 software indicates that the DFT methods do not provide systematically better NMR results than HF.<sup>16</sup> Calculations at the HF 6-31G\*/B3LYP/6-31G\* level have been recommended as the minimum model for NMR calculations, but the larger basis set with DFT was considered preferable.<sup>15,17</sup>

In this paper, we reevaluate the study of <sup>13</sup>C chemical shift calculations carried out by Cheeseman and co-workers in order to point out that, after empirical scaling, their B3LYP/6-31G\* GIAO predictions are much more successful than reported.<sup>15</sup> More importantly, we now report that accurate (rms error ~3 ppm) predictions of <sup>13</sup>C chemical shifts can be achieved for many of the common structural types of organic molecules through the use of scaled shieldings calculated from GIAO theory with a small basis set and on the basis of geometries obtained from computationally inexpensive molecular mechanics methods. GIAO calculations with different small basis sets are

compared for a new set of model compounds oriented toward organic functional groups and for which the MMX<sup>18</sup> and MM3<sup>19</sup> force fields as well as B3LYP/6-31G\* optimizations are used to provide geometries. We also examine the capability of empirically scaled GIAO shieldings obtained with MM3 geometries to satisfy the demands involved with determining structural stereochemistry.

**Scaling of GIAO Absolute Isotropic Shieldings.** Absolute shieldings predicted by ab initio methods tend to approach experimental values with increased size of the basis set and are often improved by inclusion of correlation corrections.<sup>1,7c,15</sup> The increased success depends partly on the direct effect of improved shielding calculations and partly on the indirect effect of improved molecular geometries when optimized at higher levels of theory.<sup>1</sup> The paper by Cheeseman et al. noted that shieldings from the GIAO method tended to converge more smoothly toward experimental values than the CSGT method as the basis set was increased.<sup>15</sup> Pulay and co-workers also noted the smooth convergence and that relative shieldings were reproduced well by the GIAO method, although there were some large discrepancies between predicted and observed absolute shieldings.<sup>7c</sup>

Most studies of theoretical shieldings either compare experimental absolute shieldings to calculated absolute shieldings or compare experimental chemical shifts to chemical shifts calculated from absolute shieldings by subtraction of a calculated reference. In a review chapter on shielding theory and on the IGLO method in particular, Kutzelnigg, Fleischer, and Schindler noted the inherent problem of using a calculated shielding for a reference compound in predicting chemical shifts.<sup>3</sup> Any error in the calculated shift for the single point of the reference compound will be reflected in all of the derived shifts, although subtracting the reference can also compensate for a general discrepancy in the magnitude of the predicted absolute shieldings. Another possibility is that the relative order of shifts could be predicted accurately, but the shifts might need scaling in order to provide a good match with experimental shifts. This need for scaling appears to be present in the GIAO shielding calculations reported by Cheeseman et al.<sup>15</sup>

The rms error of 12.5 ppm for <sup>13</sup>C chemical shifts that was found in GIAO predictions at the B3LYP/6-31G\*/B3LYP/6-31G\* level is worse than the 11.9 ppm rms error for GIAO-calculated shifts at the HF 6-31G\*/B3LYP/6-31G\* level.<sup>15</sup> However, it was also noted that the 6-31G\* results deviate on both sides of the experimental values, while the B3LYP/6-31G\*-predicted chemical shifts all deviate in one direction from the experimental values. It was not reported, however, that the deviations appear to increase with the magnitude of the chemical shifts, i.e., that the error is systematic and could be compensated for by empirical scaling.

Our approach in this paper is to use linear regression data to provide empirical scaling for theoretical isotropic shieldings in order to achieve more closely the level of predictive accuracy needed for practical applications of computed <sup>13</sup>C shifts. In a recent review, Chesnut demonstrated excellent correlations for isotropic shieldings obtained in Hartree–Fock GIAO calculations with both <sup>1</sup>H and <sup>13</sup>C experimental shielding data.<sup>20</sup> In particular, he showed the improvement in rms error that could be achieved by using slope-corrected shieldings in the case of

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the  $^1\text{H}$  data, compared to use of the ideal line of slope 1.0. Chesnut also noted the need to be wary of empirical corrections when the goal is theoretical understanding of nuclear shieldings. Other authors have also reported linear correlations of theoretical shieldings with experimental data.<sup>3,6c</sup>

We have reexamined the data of Cheeseman et al.<sup>15</sup> and find excellent linear correlations between experimental  $^{13}\text{C}$  chemical shifts,  $\delta_{\text{C}}$ , and theoretical absolute shieldings. In the case of GIAO shieldings from B3LYP/6-31G\*//B3LYP/6-31G\* calculations, a slope of  $-1.054$  rather than the ideal slope of  $-1.000$  is found. The rms error of points from the least-squares correlation line is only 3.9 ppm, the mean absolute deviation is 3.1 ppm, and the maximum deviation is  $-7.6$  ppm. In contrast, the analogous correlation with the Hartree-Fock GIAO 6-31G\*//B3LYP/6-31G\* shieldings gives an rms error of 7.8 ppm, a mean absolute deviation of 6.2 ppm, and a maximum deviation of 14.7 ppm. In the correlation of  $\delta_{\text{C}}$  with shieldings<sup>15</sup> from the large B3LYP/6-311+G(2d,p)//B3LYP/6-31G basis set that includes diffuse functions, the GIAO DFT data give a slope of  $-0.953$  and an rms error of only 2.5 ppm, while the HF 6-311+G(2d,p)//B3LYP data yield a slope of  $-0.890$  and an rms error of 8.0 ppm. Thus, it is clear now that accounting for electron correlation with B3LYP calculations leads to substantially better relative NMR shieldings than the Hartree-Fock calculations. Furthermore, if the slope and intercept of the least-squares correlation line were used to scale GIAO isotropic absolute shieldings,  $\sigma$ , to obtain predicted chemical shifts,  $\delta_{\text{pred}}$ , as in eq 1, then the scaled calculations would yield a much more practical level of error in computed chemical shifts than would the direct calculations where the only adjustment is subtraction of a fixed reference.

$$\delta_{\text{pred}} = m\sigma + i \quad (1)$$

For full practicality, it is desirable to use as small a basis set as possible for the GIAO calculations. Further, geometry optimizations even at the B3LYP/6-31G\* level are quite computationally expensive. Molecular mechanics calculations are enormously faster than ab initio molecular orbital calculations for geometry optimizations. Oldfield and co-workers used molecular mechanics to relax experimental protein structures before carrying out shielding calculations.<sup>6d</sup> Thus, in a preliminary survey, we examined the same set of structures used by Cheeseman et al. in single-point GIAO calculations at the B3LYP/3-21G level on geometries obtained from MMX molecular mechanics calculations. The quality of the linear correlation was distinctly poorer, with an rms error of 10.7 ppm. However, despite the substantially larger overall error, the B3LYP/3-21G//MMX results were encouraging. Most of the error came from large individual errors for a few compounds, namely the benzenium and phenonium ions,<sup>21</sup> [1.1.1]propellane,<sup>22</sup> and tetrafluoromethane, for which molecular mechanics calculations are either not parameterized or well-suited and for which molecular mechanics thus could not be expected to give good geometries. Chemical shifts in the more ordinary compounds were accounted for with much greater success.

**Scaled GIAO shieldings for a Set of Model Organic Compounds Containing C, H, O, and N.** The set of model compounds chosen by Cheeseman and co-workers included particularly challenging compounds that were known to require correlated ab initio methods either for geometry predictions or

for shielding predictions.<sup>15</sup> Most of the experimental  $^{13}\text{C}$  shift data for the small molecules were obtained in the gas phase.<sup>23</sup> We have chosen a more organic-oriented set of model structures that contain only C, H, O, and N but which includes more structural types, such as carboxylic acid, ester, amide, heteroaromatic, ether, vinyl ether, and acetal functional groups. The new set consists of 38 compounds and 76 different carbon nuclei. The model structures, listed in Table 1, are deliberately selected so as not to contain any conformationally ambiguous cases, so the side chains are restricted to methyl groups and rings are restricted to those that are well-defined, such as cyclohexane. The geometries of all of these molecules should be reasonably well described by molecular mechanics; in fact, the experimental geometries of many of the molecules were employed in the parameterization of the MMX<sup>18</sup> (most parameters are from MM2) and MM3<sup>19</sup> force fields. Furthermore, while the experimental  $^{13}\text{C}$  chemical shifts to be compared here with the theoretical shieldings were taken from a single compilation, they were obtained in a wide range of liquid phase conditions.<sup>24</sup>

Absolute shieldings were calculated for the compounds in Table 1 via the GIAO method at the HF 3-21G level with MMX geometries (3-21G//MMX) and at the B3LYP/3-21G//MMX level. GIAO calculations with MM3 geometries were carried out at the B3LYP/3-21G//MM3 and B3LYP/6-31G\*//MM3 levels. Another set of B3LYP calculations for MM3 geometries used the 3-21G basis set for carbon and hydrogen, but augmented the heteroatoms with polarization and diffuse functions, i.e., the 6-31+G\* basis set was applied to heteroatoms. We will refer to this augmented set as B3LYP/3-21G-(X, 6-31+G\*). For comparison, calculations at the B3LYP/6-31G\*//B3LYP/6-31G\* level were also carried out. The DFT calculations with the B3LYP exchange functional use a coupled perturbative scheme but do not include a magnetic field dependence in the exchange functional.<sup>16</sup> All molecular orbital calculations were carried out with the Gaussian 94 program.<sup>25</sup>

The results of the linear regression analysis comparing experimental  $^{13}\text{C}$  shifts,  $\delta_{\text{C}}$ , to GIAO absolute isotropic shieldings,  $\sigma$ , are summarized in Table 2. The  $\delta_{\text{C}}$  are listed in Table 3. The absolute shieldings in Table 1 vary substantially with the basis set. However, the linear correlations of  $\delta_{\text{C}}$  with  $\sigma$  are all excellent, as indicated by high squares of correlation coefficients,  $r^2$ , that range from 0.994 to 0.997. The statistics listed in Table 2 are more revealing than the correlation coefficients, which are not adequate to distinguish the qualities of the correlations. The rms error is particularly indicative of correlation quality. The individual deviations from the correlation line are equivalent to the difference between the predicted chemical shift after empirical scaling via eq 1 and the observed shift, i.e.,  $\Delta\delta = \delta_{\text{pred}} - \delta_{\text{C}}$ . The mean absolute deviations,  $|\Delta\delta|_{\text{av}}$ , and the number of predicted shifts which deviate by 5.0 ppm or more from experiment are also listed in Table 2.

As illustrated in Figure 1, the best correlation is obtained with shieldings calculated at the B3LYP/6-31G\*//B3LYP/6-31G\* level which give an rms error of only 3.1 ppm. The

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**Table 1.** GIAO Calculations of Isotropic  $^{13}\text{C}$  Shieldings for Compounds Containing C, H, O, and N

compd	carbon	3-21G// MMX	B3LYP/3-21G// MMX	B3LYP/3-21G// MM3	B3LYP/3-21G(X,6-31+G*)// MM3	B3LYP/6-31G*// MM3	B3LYP/6-31G*// B3LYP/6-31G*
methane	C1	207.0	199.3	199.5	199.5	188.7	193.0
ethane	C1	200.5	189.1	189.7	189.7	176.5	180.4
propane	C1	193.6	182.2	182.9	182.9	168.9	172.4
	C2	195.1	180.7	181.5	181.5	166.9	170.4
2-methylpropane	C1	187.7	176.4	176.8	176.8	162.0	165.3
	C2	191.8	175.2	175.7	175.7	161.0	163.6
2,2-dimethylpropane	C1	182.5	171.3	171.7	171.7	156.3	158.9
	C2	190.6	172.7	173.1	173.1	159.3	160.0
cyclopropane	C1	213.1	200.2	200.2	200.2	188.9	189.2
bicyclo[1.1.0]butane	C1	211.8	196.3	202.9	202.9	191.2	190.5
	C2	185.5	174.5	174.7	174.7	159.5	160.0
cyclobutane	C1	189.5	176.1	175.5	175.5	161.1	165.4
cyclohexane	C1	188.5	173.6	174.6	174.6	158.8	161.9
ethene	C1	90.1	88.2	88.2	88.2	70.4	73.7
propene	C1	96.0	93.9	94.1	94.1	76.9	79.6
	C2	83.4	80.6	80.9	80.9	60.7	63.0
	C3	190.6	179.1	179.4	179.4	165.9	169.1
2-methylpropene	C1	99.5	96.7	96.5	96.5	79.5	81.8
	C2	79.3	75.5	75.8	75.8	54.0	55.0
	C3	187.4	176.4	176.8	176.8	163.0	165.7
(E)-2-butene	C1	191.3	179.9	180.4	180.4	167.0	170.2
	C2	89.4	86.2	86.7	86.7	67.2	69.1
(Z)-2-butene	C1	196.5	185.6	186.0	186.0	173.2	175.9
	C2	91.8	88.2	88.4	88.4	69.0	70.4
ethyne	C1	142.3	140.2	139.0	139.0	128.1	128.8
allene	C1	138.3	132.7	132.2	132.2	117.8	119.5
	C2	7.7	10.6	9.9	9.9	-16.2	-12.7
benzene	C1	89.4	87.6	88.2	88.2	67.8	68.6
furan	C2	77.2	77.5	74.4	74.8	54.9	55.9
	C3	101.8	98.9	99.1	98.2	80.5	85.8
pyrrole	C2	95.2	96.4	98.8	99.0	80.8	81.8
	C3	105.7	102.6	105.3	103.5	87.1	87.5
pyridine	C2	62.8	64.1	68.0	68.4	45.1	46.3
	C3	93.0	89.9	91.9	91.0	72.0	73.2
	C4	83.1	83.5	84.6	83.1	62.4	62.4
methylamine	C1	182.9	169.8	169.4	170.1	155.8	159.1
trimethylamine	C1	170.9	158.4	158.1	157.1	141.1	144.7
acetonitrile	C1	93.6	98.1	99.5	102.3	87.3	86.9
	C2	204.6	195.4	196.0	195.8	185.3	187.8
formamide	C1	61.1	68.4	65.6	63.6	42.9	44.7
2, formamide dimer	C1			61.7	60.1	39.3	38.9
acetamide	C1	54.8	62.2	58.4	54.6	34.8	35.3
	C2	189.9	181.1	180.4	178.0	167.1	168.9
3, acetamide dimer	C1			54.5	51.4	31.4	29.9
	C2			179.7	177.3	166.4	167.7
<i>N,N</i> -dimethylformamide	C1	55.9	63.9	62.3	61.9	39.6	41.0
	<i>s</i> -CH <sub>3</sub>	178.9	168.1	173.4	173.6	158.7	160.6
	<i>a</i> -CH <sub>3</sub>	176.7	165.8	167.9	168.2	153.2	155.1
<i>N,N</i> -dimethylacetamide	C1	50.9	59.0	56.1	54.5	32.7	33.7
	C2	187.9	178.4	179.3	176.9	165.5	168.6
	<i>s</i> -CH <sub>3</sub>	176.7	165.2	171.3	171.4	156.1	158.0
	<i>a</i> -CH <sub>3</sub>	175.4	163.4	167.0	167.1	151.8	153.8
nitromethane	C1	154.6	147.1	144.0	146.4	129.7	129.8
methanol	C1	166.2	151.9	151.9	151.7	136.1	139.3
dimethyl ether	C1	159.3	144.8	145.6	145.0	128.4	131.7
oxirane	C1	181.4	166.0	166.0	166.0	151.0	149.9
1,3-dioxane	C2	132.3	113.8	113.6	114.0	93.8	97.8
	C4	157.4	140.8	140.2	139.2	121.6	125.1
	C5	188.3	174.9	175.5	173.7	159.5	162.8
2,3-dihydrofuran	C2	71.0	71.4	70.6	71.2	50.5	50.6
	C3	113.9	112.2	111.4	109.3	92.9	98.5
	C4	185.2	171.0	171.1	170.7	156.2	158.6
	C5	155.1	139.0	138.3	137.8	120.8	122.0
ethanal	C1	27.8	28.6	29.2	27.4	4.9	4.2
	C2	182.9	171.8	173.1	170.5	158.9	159.9
2-propanone	C1	183.1	173.2	174.0	171.5	160.3	161.4
	C2	22.8	24.3	24.7	22.3	-0.5	-3.0
bicyclo[2.2.1]heptan- 2-one	C1	170.8	155.1	156.3	153.5	139.5	139.2
	C2	14.6	14.1	15.2	12.8	-12.0	-14.6
	C3	174.1	160.7	160.9	158.3	144.7	145.3
	C4	182.1	165.7	166.3	165.8	150.6	152.2
	C5	186.7	172.5	171.5	171.6	156.4	160.2
	C6	191.5	177.1	175.9	174.9	161.1	163.1
	C7	179.8	165.2	165.0	164.3	149.2	151.5
acetic acid	C1	49.9	52.7	50.6	49.7	30.1	30.4
	C2	189.5	179.3	183.4	181.1	170.5	171.1
1, acetic acid dimer	C1			43.5	43.7	23.2	21.5
	C2			182.2	179.8	169.3	169.0
methyl acetate	C1	47.7	52.7	49.6	49.3	28.7	29.1
	C2	188.1	179.3	182.0	179.6	169.2	169.7
	OCH <sub>3</sub>	166.2	154.4	153.9	152.7	137.1	139.2

**Table 2.** Statistical Evaluation of Linear Correlations of Experimental  $^{13}\text{C}$  Chemical Shifts vs GIAO Isotropic Shieldings:  $\delta_{\text{C}} = m\sigma + i$ 

method	$m$	$i$	maximum $\Delta\delta$ , ppm	no. of $\Delta\delta >  5 $ ppm	$ \Delta\delta _{\text{av}}$ , ppm	rms error, ppm
(a) Monomer Data						
3-21G//MMX	-1.062	224.5	10.8	25	3.8	4.7
B3LYP/3-21G//MMX	-1.189	233.4	15.5	14	2.8	4.0
B3LYP/3-21G//MM3	-1.176	232.1	12.6	7	2.8	3.6
B3LYP/3-21G(X,6-31+G*)//MM3	-1.174	231.1	11.1	8	2.4	3.2
B3LYP/6-31G*//MM3	-1.102	203.6	11.3	9	2.8	3.7
B3LYP/6-31G*//B3LYP/6-31G*	-1.091	204.3	12.1	6	2.2	3.1
(b) Dimer-Included Data						
B3LYP/3-21G//MM3	-1.170	231.1	8.7	7	2.6	3.2
B3LYP/3-21G(X,6-31+G*)//MM3	-1.168	230.2	7.6	7	2.3	2.9
B3LYP/6-31G*//MM3	-1.097	202.8	7.9	7	2.6	3.3
B3LYP/6-31G*//B3LYP/6-31G*	-1.084	203.1	8.7	3	1.9	2.5

B3LYP/3-21G(X,6-31+G\*)//MM3 calculations are almost as good, with an rms error of 3.2 ppm for the correlation shown in Figure 2. Although not as successful, the predicted shieldings obtained with B3LYP/3-21G and B3LYP/6-31G\* calculations based on MM3 geometries also have rms errors of less than 4.0 ppm in the linear regression. The B3LYP/3-21G//MMX results are not as good as the comparable MM3-based calculations, and the HF 3-21G//MMX calculations are distinctly worse. The slopes of the correlation lines indicate that GIAO B3LYP/3-21G shieldings require empirical scaling by about 17% and B3LYP/6-31G\* shieldings need scaling by about 9% to match the range of experimental shifts.

The GIAO calculations based on molecular mechanics geometries are worth discussing in more detail because the computer time to carry out an MMX or MM3 geometry optimization is negligible compared to the time required for a single-point ab initio or DFT MO calculation plus the GIAO calculation. The single-point plus GIAO calculations in turn are much faster than the B3LYP/6-31G\* geometry optimizations. The time savings will vary tremendously, depending upon the size of the system and the number of steps in the optimization process. As a minimal example, the B3LYP/6-31G\* geometry optimization of bicyclo[2.2.1]heptan-2-one finished in only six steps, a relatively small number. The B3LYP/3-21G//MM3 GIAO calculation took only 8%, the B3LYP/3-21G(X,6-31+G\*)//MM3 calculation, 13%; and the B3LYP/6-31G\*//MM3 calculation, 25% as much time as the B3LYP/6-31G\*//B3LYP/6-31G\* calculation for this molecule. Many molecules require many more than six steps in the optimization, especially larger and more flexible molecules, so the time savings will often be substantially greater.

The GIAO 3-21G//MMX calculations that do not include the effects of electron correlation are the least successful. The 3-21G//MMX correlation of experimental shifts with shieldings has an rms error of 4.7 ppm, and 25 (or about one-third) of the calculated shifts are off by  $\geq 5.0$  ppm. The HF 3-21G results would be better described by two separate correlations for the  $\text{sp}^3$  and  $\text{sp}^2$  carbons, each having a slope steeper than the overall  $-1.06$  slope listed in Table 2.

As shown in Table 2, the GIAO B3LYP/3-21G-calculated shieldings based on MMX geometries give a larger rms error of 4.0 ppm, but the same  $|\Delta\delta|_{\text{av}}$  for scaled  $\delta_{\text{pred}}$  of 2.8 ppm as for the B3LYP/3-21G//MM3 calculation. For MMX, 14 of the scaled  $\delta_{\text{pred}}$  differ from experimental  $\delta_{\text{C}}$  by more than 5.0 ppm. All seven of the points in the MM3 correlation that deviate by more than 5 ppm are worse in the MMX-based calculations. Several additional  $\text{sp}^2$ -hybridized carbons deviate more in the MMX-based calculations. However, the alkyl carbons are treated just as well in the calculations based on MMX geometries as those based on MM3.

The rms error for deviations from the correlation line for the B3LYP/3-21G//MM3 shieldings is 3.6 ppm, a substantial improvement over the comparable calculations based on MMX geometries. Clearly, the more refined force field and parameterization of the MM3 method is helpful, particularly in regard to  $\text{sp}^2$  carbons and especially heteroaromatic rings.<sup>26</sup> Nevertheless, deviations tend to be larger for the  $\text{sp}^2$  carbons. The mean absolute error in comparing  $\delta_{\text{pred}}$  from B3LYP/3-21G//MM3 calculations to experimental  $\delta_{\text{C}}$  is 2.8 ppm. Only seven entries deviate by  $\geq |5|$  ppm from experiment: the carbonyl carbons of the primary amides, formamide and acetamide are predicted to be more shielded than observed; terminal C2 carbons of propene and isobutene, the central C2 of allene, and C3 of furan are predicted to be too deshielded; and  $\delta_{\text{pred}}$  for the methylene C2 of bicyclo[1.1.0]butane is too shielded. Only one of these more deviant points is for a saturated, tetracoordinate carbon, and if only alkyl carbons are considered, the rms error for the correlation drops to 2.5 ppm with a  $|\Delta\delta|_{\text{av}}$  of 2.1 ppm.

Increasing the basis set to 6-31G\* in the B3LYP/6-31G\*//MM3 GIAO calculations does not yield better results statistically than the B3LYP/3-21G calculations, as seen in Table 2, although the slope of the correlation line indicates the absolute shieldings require less scaling. However, the pattern of points that deviate by  $\geq 5.0$  ppm is now very similar to that found for the B3LYP/6-31G\*//B3LYP/6-31G\* calculations shown in Figure 1. The six points that deviate most in both sets are for the carbonyl carbons of formamide, acetamide, and acetic acid and the  $\text{sp}$ -hybridized carbons of acetonitrile, acetylene, and allene. Additionally, C2 of bicyclo[1.1.0]butane, the methyl carbon of acetic acid, and C2 of 1,3-dioxane also deviate by  $\geq 5.0$  ppm in the B3LYP/6-31G\*//MM3 calculations. All of these most deviant points, except C2 of 1,3-dioxane and C2 of allene, are predicted to be too shielded.

In changing from MM3 geometries to B3LYP/6-31G\* geometries, there are some significant improvements in the GIAO B3LYP/6-31G\* predictions. Improvements of over 2.0 ppm are found for the strained ring systems (cyclopropane, bicyclo[1.1.0]butane, cyclobutane, and oxirane), ethene, C3 of furan, and C2 of 1,3-dioxane. Although there are numerous other smaller changes in both directions, overall 70% of the data points fit better, leading to the rms error of 3.1 ppm and  $|\Delta\delta|_{\text{av}}$  of 2.2 ppm for the B3LYP/6-31G\*//B3LYP/6-31G\* model.

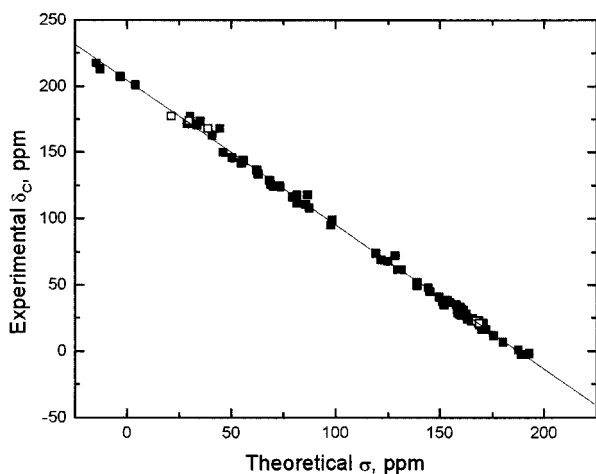
Keeping in mind the strategy of using a small basis set with molecular mechanics geometries, we investigated the idea of a locally dense basis set,<sup>6c,20,27</sup> applied only to heteroatoms. The B3LYP/3-21G(X,6-31+G\*)//MM3 combination, as noted ear-

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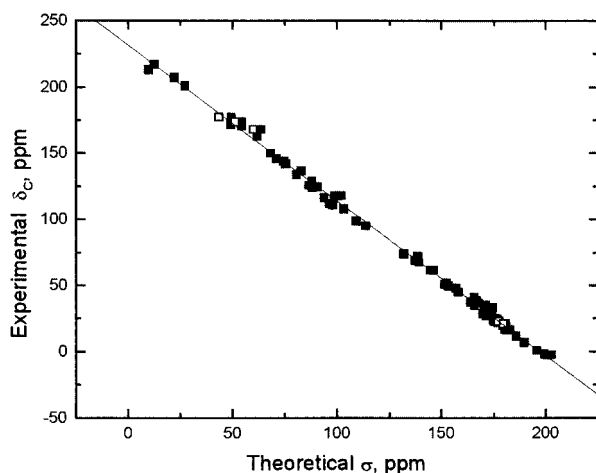
**Table 3.** Experimental<sup>a</sup> and Predicted<sup>b</sup> <sup>13</sup>C Chemical Shifts for Compounds Containing C, H, O, and N

compd	carbon	B3LYP/3-21G(X,6-31+G*)/MM3		B3LYP/6-31G*/B3LYP/6-31G*		expt $\delta_c$ , ppm
		$\delta_{\text{pred}}$ , ppm	$\Delta\delta^c$ , ppm	$\delta_{\text{pred}}$ , ppm	$\Delta\delta^c$ , ppm	
methane	C1	-2.9	-0.6	-6.0	-3.7	-2.3
ethane	C1	8.6	2.1	7.6	1.1	6.5
propane	C1	16.5	0.4	16.3	0.2	16.1
	C2	18.1	1.8	18.5	2.2	16.3
2-methylpropane	C1	23.6	0.3	24.0	0.7	23.3
	C2	24.9	0.3	25.8	1.2	24.6
2,2-dimethylpropane	C1	29.6	-1.8	30.9	-0.5	31.4
	C2	27.9	0.5	29.7	2.3	27.4
cyclopropane	C1	-3.7	-0.9	-1.9	0.9	-2.8
bicyclo[1.1.0]butane	C1	-6.9	-3.9	-3.3	-0.3	-3.0
	C2	26.1	-6.9	29.7	-3.3	33.0
cyclobutane	C1	25.1	2.7	23.9	1.5	22.4
cyclohexane	C1	26.2	-0.8	27.7	0.7	27.0
ethene	C1	127.1	3.6	123.3	-0.2	123.5
propene	C1	120.3	4.4	116.9	1.0	115.9
	C2	135.7	2.3	134.9	1.5	133.4
	C3	20.6	1.2	19.9	0.5	19.4
2-methylpropene	C1	117.4	6.1	114.5	3.2	111.3
	C2	141.6	-0.2	143.5	1.7	141.8
	C3	23.6	-0.6	23.6	-0.6	24.2
(E)-2-butene	C1	19.4	2.6	18.7	1.9	16.8
	C2	128.9	3.5	128.2	2.8	125.4
(Z)-2-butene	C1	12.9	1.5	12.5	1.1	11.4
	C2	126.9	2.7	126.8	2.6	124.2
ethyne	C1	67.8	-4.1	63.5	-8.4	71.9
allene	C1	75.7	2.2	73.6	0.1	73.5
	C2	218.6	6.0	216.9	4.3	212.6
benzene	C1	127.1	-1.4	128.8	0.3	128.5
furan	C2	142.8	-0.8	142.6	-1.0	143.6
	C3	115.5	5.1	110.1	-0.3	110.4
pyrrole	C2	114.6	-2.7	114.5	-2.8	117.3
	C3	109.2	1.6	108.3	0.7	107.6
pyridine	C2	150.3	0.7	153.0	3.4	149.6
	C3	123.9	-0.3	123.8	-0.4	124.2
	C4	133.1	-3.1	135.5	-0.7	136.2
methylamine	C1	31.5	3.2	30.7	2.4	28.3
trimethylamine	C1	46.7	-0.8	46.3	-1.2	47.5
acetonitrile	C1	110.7	-7.0	109.0	-8.7	117.7
	C2	1.5	1.2	-0.4	-0.7	0.3
2, formamide dimer	C1	160.0	-7.6	161.0	-6.6	167.6
3, acetamide dimer	C1	170.2	-3.2	170.7	-2.7	173.4
	C2	23.0	0.4	21.4	-1.2	22.6
N,N-dimethylformamide	C1	157.8	-4.8	158.7	-3.9	162.6
	s-CH <sub>3</sub>	27.3	-4.2	29.1	-2.4	31.5
	a-CH <sub>3</sub>	33.7	-2.8	35.0	-1.5	36.5
N,N-dimethylacetamide	C1	166.5	-3.9	166.6	-3.8	170.4
	C2	23.5	2.0	20.4	-1.1	21.5
	s-CH <sub>3</sub>	29.9	-5.1	31.9	3.1	35.0
	a-CH <sub>3</sub>	34.9	-3.1	36.5	-1.5	38.0
nitromethane	C1	59.2	-2.0	62.5	1.3	61.2
methanol	C1	52.9	2.4	52.2	1.7	50.5
dimethyl ether	C1	60.8	-0.4	60.4	-0.8	61.2
oxirane	C1	36.3	-4.3	40.7	0.1	40.6
1,3-dioxane	C2	97.0	2.2	97.1	2.3	94.8
	C4	67.5	0.0	67.6	0.1	67.5
	C5	27.2	-0.3	26.7	-0.8	27.5
2,3-dihydrofuran	C2	147.0	1.4	148.3	2.7	145.6
	C3	102.5	4.1	96.4	-2.0	98.4
	C4	30.8	2.3	31.2	2.7	28.5
	C5	69.2	0.6	70.9	2.3	68.6
ethanal	C1	198.2	-2.3	198.6	-1.9	200.5
	C2	31.0	-0.2	29.8	-1.4	31.2
2-propanone	C1	29.8	-0.9	28.2	-2.5	30.7
	C2	204.1	-2.6	206.4	-0.3	206.7
bicyclo[2.2.1]heptan-2-one	C1	50.9	1.6	52.3	3.0	49.3
	C2	215.3	-1.5	219.0	2.2	216.8
	C3	45.2	0.5	45.7	1.0	44.7
	C4	36.5	1.7	38.2	3.4	34.8
	C5	29.8	3.1	29.5	2.8	26.7
	C6	25.8	2.1	26.4	2.7	23.7
	C7	38.3	1.2	38.9	1.8	37.1
1, acetic acid dimer	C1	179.2	2.3	179.8	2.9	176.9
	C2	20.1	-0.7	20.0	-0.8	20.8
methyl acetate	C1	172.6	1.3	171.6	0.3	171.3
	C2	20.3	-0.3	19.2	-1.4	20.6
	OCH <sub>3</sub>	51.8	0.3	52.3	0.8	51.5

<sup>a</sup> Reference 24. <sup>b</sup> Calculated with eq 1, using slopes and intercepts from Table 2 for dimer-included data. <sup>c</sup>  $\Delta\delta = \delta_{\text{pred}} - \delta_c$ .



**Figure 1.** Plot of experimental  $^{13}\text{C}$  chemical shifts vs theoretical isotropic shieldings from GIAO B3LYP/6-31G\*/B3LYP/6-31G\* calculations for the 38 organic compounds in Table 1. Open squares represent data for dimers **1**, **2**, and **3** that were not used in determining the correlation line shown.

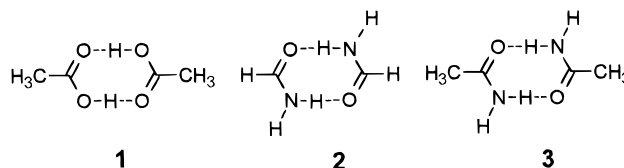


**Figure 2.** Plot of experimental  $^{13}\text{C}$  chemical shifts vs theoretical isotropic shieldings from GIAO B3LYP/3-21G(X,6-31+G\*)/MM3 calculations for the 38 organic compounds in Table 1. Open squares represent data for dimers **1**, **2**, and **3** that were not used in determining the correlation line shown.

lier, gives results nearly as good as those from the B3LYP/6-31G\*/B3LYP/6-31G\* method. The rms error is 3.2 ppm,  $|\Delta\delta|_{\text{av}}$  is 2.4 ppm, and eight points have  $|\Delta\delta| \geq 5.0$  ppm. Of course, whether the heteroatom-augmented basis set qualifies as a small basis set depends on the ratio of carbon to heteroatoms. If this ratio is high, 3-21G(X,6-31+G\*) is a small basis set. If the number of carbons and heteroatoms is equal, the total number of basis functions for a molecule will be almost equivalent to the total for the 6-31G\* basis set.

The  $^{13}\text{C}$  shifts of the carbonyl carbon of acetic acid and the primary amides, formamide and acetamide, are not predicted well by any of the methods in Table 1. Since the corresponding ester and tertiary amides, i.e., methyl acetate, *N,N*-dimethylformamide, and *N,N*-dimethylacetamide, fare better in the predictions, we investigated whether inclusion of hydrogen bonding with the former structures might correct some of the discrepancy. The dependence of  $\delta_{\text{C}}$  for acetic acid on dimer formation has been known for many years.<sup>28</sup> It has also been recently shown that hydrogen bonding needs to be included in order for GIAO ab initio shieldings to properly predict both isotropic and anisotropic shielding tensors for  $^{15}\text{N}$  in benza-

mid.<sup>29</sup> Oldfield has also included hydrogen bonding in calculations of chemical shifts in model peptides.<sup>6</sup> Accordingly, we calculated GIAO shieldings for the H-bonded dimer structures **1–3**. These shieldings are listed in Table 1 below the data for the monomers. Obviously, hydrogen bonding leads to deshielding in the predictions and a closer match to experiment for both the carbonyl and methyl carbons, as indicated in Table 2 by the “dimer-included” linear regression analysis. The better fit of these dimer data is shown in Figures 1 and 2.



The two best methods of those examined here for predicting relative shieldings are the B3LYP/3-21G(X,6-31+G\*)/MM3 and B3LYP/6-31G\*/B3LYP/6-31G\* GIAO calculations. For the dimer-included data in which the calculated shieldings for dimers **1–3** replace the monomer values, the rms errors in the correlation of  $\delta_{\text{C}}$  with  $\sigma$  are only 2.9 ppm for B3LYP/3-21G(X,6-31+G\*)/MM3 and 2.5 ppm for B3LYP/6-31G\*/B3LYP/6-31G\*. The improvements come not only from the movement of the carbonyl data closer to the regression lines but also from the small changes in the slope and intercept that reduce slightly the deviations of many other data points. For this reason, the dimer-included linear regression data are to be preferred for use in subsequent predictions from eq 1.

The predicted shifts,  $\delta_{\text{pred}}$ , calculated from eq 1 from the dimer-included data are listed in Table 3 for the two best methods. The individual  $\Delta\delta$  values are also given. For B3LYP/3-21G(X,6-31+G\*)/MM3 calculations, the  $|\Delta\delta|_{\text{av}}$  is 2.3 ppm and seven  $\Delta\delta$  are  $\geq 5.0$  ppm. The seven most deviant points are for C2 of bicyclobutane, C1 of 2-methylpropene, C2 of allene, C3 of furan, C1 of acetonitrile, C1 of formamide dimer, and the methyl syn to the carbonyl oxygen of *N,N*-dimethylacetamide. The amide carbonyls in the dimers **2** and **3** are still predicted to be too shielded, but by amounts similar to those for the tertiary amides *N,N*-dimethylformamide and *N,N*-dimethylacetamide. (In the monomers,  $\Delta\delta$  for formamide and acetamide are  $-11.1$  and  $-6.3$  ppm, respectively.) The *N*-methyls in the tertiary amides are also predicted to be too shielded and are among some of the more deviant alkyl points. Unfortunately, the  $\delta_{\text{C}}$  of amides and peptides are difficult to predict accurately, since the calculated shifts are quite sensitive to C–O and C–N bond lengths and pyramidalicity at nitrogen, in addition to hydrogen bonding.<sup>6</sup> For the B3LYP/6-31G\*/B3LYP/6-31G\* calculations, the dimer-included data give a  $|\Delta\delta|_{\text{av}}$  of 1.9 ppm, and only three points deviate by  $\geq 5.0$  ppm: acetylene, acetonitrile, and formamide.

The scaled GIAO B3LYP/3-21G(X,6-31+G\*)/MM3 shieldings adequately account (rms error  $\sim 3$  ppm) for the  $^{13}\text{C}$  shifts of carbon nuclei that occur in a variety of common functional groups containing C, H, O, and N atoms and in simple alkyl groups. This is remarkable, especially considering that the experimental data were obtained in a variety of solution conditions. It is not unusual for chemical shifts to differ by several ppm between the gas phase and solution, or to differ by 1–2 ppm for different solutions. For example, C2 of allene is less shielded by about 5 ppm in the gas phase while C2 of 2-propanone (acetone) is more shielded by about 5.5 ppm in

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the gas phase compared to solution.<sup>23</sup> It is likely that the linear regression approach to empirical scaling compensates somewhat for the change in phase. There is clearly room for improvement, perhaps especially by refining the molecular mechanics method for amides.<sup>30</sup> A higher basis set with diffuse functions for carbon would likely remove the problems with alkene and alkyne shieldings, but at considerable computational cost.

To be truly practical, this approach of using scaled GIAO shieldings and geometries from molecular mechanics must also accurately predict the chemical shift variations associated with different conformations or relative configurations; the issues involved are addressed in the next section.

**Conformation and Relative Configuration from <sup>13</sup>C Chemical Shifts.** Most of the current practical applications of <sup>13</sup>C shifts to conformational or configurational questions arise from the  $\gamma$ -substituent effect.<sup>31</sup> A carbon under consideration, C $\alpha$ , will be more shielded when a substituent attached at a  $\gamma$ -position is oriented in a syn or gauche alignment than when the alignment is anti. For a C $\alpha$ -C $\beta$ -C $\gamma$ -X fragment, where X = CH<sub>3</sub>, OH, NH<sub>2</sub>, Cl, or Br, a strong dependence on dihedral angle occurs, such that the  $\gamma$ -effect is about -10 to -5 ppm for dihedral angles of 0-60°, -5 to -2 ppm for angles between 60° and 120°, and about -2 to +2 ppm in the range 120-180°. The same relation generally holds for 1,2-disubstituted alkenes, allowing *Z* and *E* configurations to be distinguished by the more shielding experienced by C $\alpha$  in the *Z* isomer of a C $\alpha$ -C=C-X fragment.<sup>24</sup>

The stereochemistry of substituent placement on a carbon framework is also reflected in  $\alpha$ -,  $\beta$ -, and  $\delta$ -substituent effects, for example, as seen below in the variation of substituent effects between axial and equatorial attachment in cyclohexanes, but the stereochemical dependencies of these effects are not as readily transferred among different molecular frameworks.<sup>31</sup> Whitesell and Minton suggested that the  $\alpha$ - and  $\beta$ -substituent effects depend on the number of anti, vicinal hydrogen-hydrogen interactions experienced by the  $\alpha$ - and  $\beta$ -carbons, rather than the spatial relationship between the substituent and these carbons.<sup>32</sup>

In the present paper, we take the approach of predicting shifts for molecules by scaling GIAO-calculated isotropic shieldings via eq 1. Specifically in this section, we will focus on B3LYP/3-21G(X,6-31+G\*)/MM3 calculations; hence, the  $\delta_{\text{pred}}$  will be from eq 2, the appropriate scaling equation for these calculations:

$$\delta_{\text{pred}} = -1.168\sigma + 230.2 \quad (2)$$

Barfield and co-workers previously examined the capability of IGLO calculations to predict  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -substituent effects by using substituted butanes as model systems.<sup>33</sup> Here, the success in dealing with substituent effects and their stereochemical dependence will be evident in the examples discussed below.

In Tables 1 and 3, only the data for the *Z* and *E* isomers of 2-butene are relevant to the issue of configuration or conformation. However, the example of the 2-butenes serves nicely to illustrate the issues involved with practical application of computed <sup>13</sup>C chemical shifts to stereochemical questions. The first item to note is that the  $\delta_{\text{C}}$  for the 2-butenes differ depending

upon the literature source, with the values in Table 3 falling in the middle of the range. Relative shifts and shift differences remain about the same, but other compilations report shifts averaging from 0.6 ppm lower<sup>34</sup> to 0.6 ppm higher.<sup>35</sup> In matching experimental shifts to computed shifts, differences in solvent or referencing can change the magnitude of the  $\Delta\delta$  values, even when relative shifts are accurately predicted. For this reason, linear regression analysis will again be used as part of the data analysis in molecules more complex than the 2-butenes so that the intercept can compensate for solvent or referencing changes. The slope of a correlation between  $\delta_{\text{C}}$  and  $\delta_{\text{pred}}$  should be near 1.0.

Note that in Table 3 the chemical shift trends for the 2-butenes are reproduced well in B3LYP/3-21G(X,6-31+G\*)/MM3 calculations. The correct order of shifts is given, and both the methyl and alkene carbons of (*Z*)-2-butenes are correctly predicted to be more shielded than the corresponding nuclei in (*E*)-2-butene. Certainly, empirical knowledge of the  $\gamma$ -substituent effect would allow the isomers to be distinguished without recourse to the calculations, although the calculations could substitute for the empirical generalization. However, in a practical question of stereochemistry or conformation, often only a single synthesized or isolated structure is available for measurements. This is the situation in which accurately computed <sup>13</sup>C shifts could be of enormous practical value.

In the case of the 2-butenes, if the *Z* isomer were the only available isomer, it would be readily identified as such by comparison of the observed  $\delta_{\text{C}}$  of 11.4 and 124.2 ppm with the B3LYP/3-21G(X,6-31+G\*)/MM3  $\delta_{\text{pred}}$  of 12.9 and 126.9 ppm for the *Z* isomer vs 19.4 and 128.9 ppm predicted for the *E* isomer. The average difference,  $|\Delta\delta|_{\text{av}}$ , between observed and predicted shifts is 2.1 ppm for the match with the *Z* isomer, and 6.4 ppm for the *E* isomer. *Note, however, that if only the E isomer were available, the wrong identification would be made through the match with B3LYP/3-21G(X,6-31+G\*)/MM3-computed shifts.* The observed  $\delta_{\text{C}}$  are 16.8 and 125.4 ppm for (*E*)-2-butene, leading to a  $|\Delta\delta|_{\text{av}}$  of 3.0 ppm for the match with  $\delta_{\text{pred}}$  for (*E*)-2-butene, and only 2.7 ppm for the mismatch with  $\delta_{\text{pred}}$  for (*Z*)-2-butenes. Thus, even though the GIAO B3LYP/3-21G(X,6-31+G\*)/MM3 calculations correctly give relative shifts and the direction and approximate magnitude of the  $\gamma$ -substituent effect with a predicted -6.5 vs observed -5.4 ppm shift of the (*Z*)-2-butene methyl signal compared to the (*E*)-2-butene methyl, the errors in  $\delta_{\text{pred}}$  of  $\leq|3.5|$  ppm are enough to render the calculations inadequate for the proper identification of the *E*-alkene. The small difference between  $|\Delta\delta|_{\text{av}}$  for the correct match and  $|\Delta\delta|_{\text{av}}$  for the mismatch compared to the magnitude of  $|\Delta\delta|_{\text{av}}$  in this case, as well as the position of the observed  $\delta_{\text{C}}$  between the two sets of  $\delta_{\text{pred}}$  values for the two isomers, must be taken as warnings of a possibly unreliable outcome. (Note that the more deshielded set<sup>35</sup> of  $\delta_{\text{C}}$  would lead to a correct match.) The correct choice does emerge at the B3LYP/6-31G\*/B3LYP/6-31G\* level, where the  $\delta_{\text{C}}$  for (*E*)-2-butene match with  $\delta_{\text{pred}}$  with a  $|\Delta\delta|_{\text{av}}$  of 2.0 ppm, while the mismatch with the (*Z*)-2-butene  $\delta_{\text{pred}}$  gives a  $|\Delta\delta|_{\text{av}}$  of 2.8 ppm.

For more complex systems, we propose three criteria to judge the quality of the match between  $\delta_{\text{C}}$  and  $\delta_{\text{pred}}$  for various possible structures: (1) individual deviations,  $\Delta\delta$ , between  $\delta_{\text{C}}$  and  $\delta_{\text{pred}}$  should be less than  $|5.0|$  ppm for alkyl carbons; (2) the mean absolute deviation,  $|\Delta\delta|_{\text{av}}$ , should be 2.5 ppm or less; and (3) the rms error from a linear regression analysis of the

(34) Breitmaier, E.; Voelter, W. *<sup>13</sup>C NMR Spectroscopy*, 2nd ed.; Verlag Chemie: New York, 1978; p 138.

(35) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 5th ed.; Wiley: New York, 1991; p 238.

(30) Allinger has suggested that further improvements in the MM3 forcefield for amides are possible: Lii, Y.-H.; Allinger, N. L. *J. Comput. Chem.* **1991**, *12*, 186.

(31) All reference texts on <sup>13</sup>C chemical shifts discuss the  $\gamma$ -substituent effect. For more detailed discussions, see: (a) Dudgeon, H. *Top. Stereochem.* **1986**, *16*, 219. (b) Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman Hall: New York, 1987. (c) Pihlaja, K.; Kleinpeter, E. *Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis*; VCH: New York, 1994.

(32) Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1987**, *109*, 225.

(33) Barfield, M. *J. Am. Chem. Soc.* **1995**, *117*, 2862.



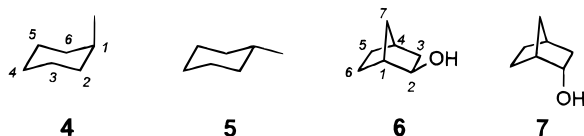
**Table 4.** Experimental<sup>a</sup> and Predicted<sup>b</sup>  $^{13}\text{C}$  Chemical Shifts for **4** and **5**

	<b>4</b>		<b>5</b>	
	$\delta_{\text{pred}}$	$\delta_{\text{C}}$	$\delta_{\text{pred}}$	$\delta_{\text{C}}$
C1	28.11	27.58	32.64	33.18
C2,6	30.78	31.86	34.01	35.45
C3,5	20.95	20.66	26.61	26.68
C4	26.37	27.18	26.05	26.32
$\text{CH}_3$	17.54	17.29	23.43	23.36

<sup>a</sup> Reference 35. <sup>b</sup> From eq 2 and GIAO B3LYP/3-21G(X,6-31+G\*)//MM3 calculations.

correlation between  $\delta_{\text{C}}$  and  $\delta_{\text{pred}}$  should be less than 2.0 ppm and should be used as the most reliable method to distinguish among possible structures which meet the first two criteria. The second two criteria are based on experience with the examples below and with other examples as well as with our assessment of the level of accuracy needed for distinguishing between possible stereoisomers or conformations. If these levels cannot be achieved, then either the structure has not been adequately described or the scaled GIAO shielding calculations are not accurate enough to permit reliable stereochemical application for that particular type of structure. The first criterion is proposed because an individual 5.0 ppm deviation for an alkyl carbon is about two standard deviations beyond what was achieved in Table 3. In Table 3, C2 of bicyclobutane is the only alkyl carbon that deviates by more than 5.0 ppm in the B3LYP/3-21G(X,6-31+G\*)//MM3 results.

The axial and equatorial methylcyclohexanes, **4** and **5**, serve as an example where GIAO B3LYP/3-21G(X,6-31+G\*)//MM3 predictions are accurate and fully adequate to serve as the basis for a conformational assignment. Squillacote and co-workers determined the  $^{13}\text{C}$  chemical shifts at low temperature.<sup>36</sup> The  $\gamma$ -substituent effect leads to shielding of about 6 ppm at the methyl and C3,5 in **4** compared to **5**, but C1 and C2,6 shifts also differ by several ppm between the two conformers. The experimental  $\delta_{\text{C}}$  and  $\delta_{\text{pred}}$  from applying eq 2 to shieldings from B3LYP/3-21G/MM3 calculations are listed for **4** and **5** in Table 4. The  $\delta_{\text{pred}}$  match  $\delta_{\text{C}}$  very well for both conformers. The  $|\Delta\delta|_{\text{av}}$  for individual shifts are 0.59 ppm in **4** and 0.48 ppm in **5**, and the maximum error in either is 1.44 ppm. In contrast, the incorrect match of  $\delta_{\text{C}}$  for **4** to  $\delta_{\text{pred}}$  for **5** produces a  $|\Delta\delta|_{\text{av}}$  of 4.1 ppm. The analogous mismatch for **5** to  $\delta_{\text{pred}}$  for **4** gives a  $|\Delta\delta|_{\text{av}}$  of 4.3 ppm. Statistics for the matches and mismatches of methylcyclohexane conformers are given in Table 5.



Another pair of structures in which the  $\gamma$ -substituent effect is important are the isomeric 2-norbornanols: *exo*-bicyclo[2.2.1]heptan-2-ol, **6**, and *endo*-bicyclo[2.2.1]heptan-2-ol, **7**. The shielding differences between **6** and **7** are more subtle than between **4** and **5**, with the largest difference being 4.5 ppm at C6. These structures also introduce the problem of conformational mobility that is a challenging aspect of making practical use of computed  $^{13}\text{C}$  chemical shifts. The observed  $\delta_{\text{C}}$  for many molecules are time-averaged values from weighted averages of contributing conformations. This problem is encountered even in the seemingly simple case of a hydroxyl substituent on a

**Table 5.** Statistics for Conformer or Isomer Matches and Mismatches of Experimental  $\delta_{\text{C}}$  with  $\delta_{\text{pred}}$  from B3LYP/3-21G(X,6-31+G\*)//MM3 Calculations

structure		linear regression				
$\delta_{\text{C}}$	$\delta_{\text{pred}}$	maximum $ \Delta\delta $	$ \Delta\delta _{\text{av}}$	$m$	$i$	rms error
<b>4</b>	<b>4</b>	1.1	0.5	1.077	-1.7	0.7
<b>4</b>	<b>5</b>	5.8	4.3	0.840	8.2	2.6
<b>5</b>	<b>5</b>	1.4	0.5	1.116	-2.9	0.3
<b>5</b>	<b>4</b>	6.1	4.1	1.093	-6.3	3.6
<b>6</b>	<b>6a</b>	2.8	1.4	0.969	0.1	1.2
<b>6</b>	<b>6b</b>	2.8	1.4	0.989	-1.0	1.0
<b>6</b>	<b>6c</b>	3.0	1.4	0.981	-0.6	1.2
<b>6</b>	( <b>6a</b> + <b>6b</b> )/2	2.2	1.3	0.981	-0.5	0.5
<b>6</b>	( <b>7a</b> + <b>7b</b> )/2	3.3	1.9	1.013	-1.1	2.4
<b>7</b>	<b>7a</b>	3.5	1.3	1.006	-1.5	1.3
<b>7</b>	<b>7b</b>	2.6	1.0	0.996	-0.7	1.1
<b>7</b>	<b>7c</b>	4.1	1.5	0.994	-1.1	1.6
<b>7</b>	( <b>7a</b> + <b>7b</b> )/2	2.3	1.1	1.005	-1.3	0.8
<b>7</b>	( <b>6a</b> + <b>6b</b> )/2	6.2	3.0	0.948	0.3	3.4
<b>8</b>	<b>8a</b>	4.8	1.4	0.997	-0.8	1.8
<b>8</b>	( <b>9a</b> + <b>9b</b> )/2	6.8	2.2	0.998	-1.1	2.7
<b>9</b>	<b>9a</b>	6.1	1.4	0.996	-0.7	1.8
<b>9</b>	<b>9b</b>	5.9	1.7	0.998	-1.2	1.8
<b>9</b>	( <b>9a</b> + <b>9b</b> )/2	6.0	1.5	0.997	-1.0	1.8
<b>9</b>	<b>8a</b>	7.6	2.5	0.994	-0.6	3.4
<b>10(DMSO)</b>	<b>10a</b>	3.2	1.4	1.000	-1.3	1.1
<b>10(DMSO)</b>	<b>10b</b>	3.7	1.6	1.003	-1.4	1.4
<b>10(DMSO)</b>	( <b>10a</b> + <b>10b</b> )/2	3.2	1.4	1.002	-1.4	1.1
<b>10(DMSO)</b>	<b>10tb</b>	5.9	2.0	1.006	-1.4	2.3
<b>10(CDCl<sub>3</sub>)</b>	<b>10tb</b>	2.8	1.3	1.010	-1.2	1.3
<b>10(CDCl<sub>3</sub>)</b>	( <b>10a</b> + <b>10b</b> )/2	3.4	1.3	1.004	-1.1	1.3

**Table 6.** Experimental<sup>a</sup>  $\delta_{\text{C}}$  for **6** and Predicted<sup>b</sup> Shifts for Conformers **6a**, **6b**, and **6c**

	$\delta_{\text{pred}}$				<b>6</b> , $\delta_{\text{C}}$
	<b>6a</b>	<b>6b</b>	<b>6c</b>	( <b>6a</b> + <b>6b</b> )/2	
C1	47.3	44.7	45.5	46.0	44.5
C2	76.7	76.4	76.4	76.6	74.4
C3	41.4	45.2	45.4	43.3	42.4
C4	36.3	36.7	36.3	36.5	35.8
C5	30.2	30.1	29.2	30.2	28.8
C6	26.1	27.1	27.6	26.6	24.9
C7	35.4	35.3	35.0	35.3	34.6

<sup>a</sup> Reference 24. <sup>b</sup> From eq 2 and GIAO B3LYP/3-21G(X,6-31+G\*)//MM3 calculations.

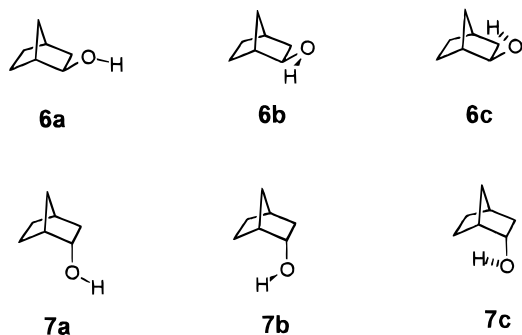
**Table 7.** Experimental<sup>a</sup>  $\delta_{\text{C}}$  for **7** and Predicted<sup>b</sup> Shifts for Conformers **7a**, **7b**, and **7c**

	$\delta_{\text{pred}}$				<b>7</b> , $\delta_{\text{C}}$
	<b>7a</b>	<b>7b</b>	<b>7c</b>	( <b>7a</b> + <b>7b</b> )/2	
C1	43.0	44.3	44.0	43.7	43.1
C2	73.6	74.2	74.0	73.9	72.5
C3	43.1	39.2	43.7	41.2	39.6
C4	38.7	38.0	38.2	38.4	37.7
C5	31.4	31.0	31.1	31.2	30.3
C6	22.3	23.0	22.7	22.7	20.4
C7	37.9	37.9	37.2	37.9	37.8

<sup>a</sup> Reference 24. <sup>b</sup> From eq 2 and GIAO B3LYP/3-21G(X,6-31+G\*)//MM3 calculations.

fixed bicyclic framework. The hydroxyl proton in any alcohol can occupy three different positions associated with the energy minima in rotation about the C—O bond. For example, **6** and **7** each give three conformers, shown as **6a–c**, and **7a–c**. The alignment of the proton has a significant effect on the C1, C2, and C3 chemical shifts and lesser effects on others, as can be seen in Tables 6 and 7 in the predictions from scaled GIAO calculations at the B3LYP/3-21G(X,6-31+G\*)//MM3 level.

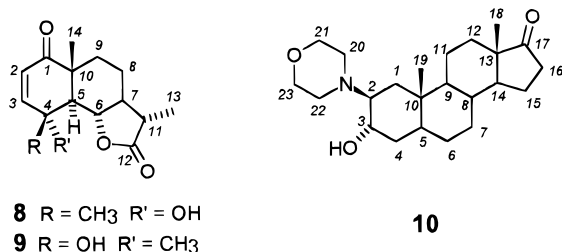
(36) Squillacote, M. E.; Neth, J. M. *Magn. Reson. Chem.* **1987**, *25*, 53.



One approach to weighting the contributions of different conformers is to use the relative energies from the molecular mechanics calculations. MM3 gives **6a** and **6b** as isoenergetic and the more crowded **6c** as 1.4 kcal/mol higher. Similarly, **7a** and **7b** are isoenergetic, and **7c** is 1.7 kcal/mol higher. Here, we simply neglect the more crowded conformers to obtain the predicted shifts as the average of **6a** and **6b** or **7a** and **7b**, as listed in Tables 6 and 7. For both **6** and **7**, the averaged  $\delta_{\text{pred}}$  fit the data better than do the  $\delta_{\text{pred}}$  from any of the individual conformers **6a–c** or **7a–c**, judging by the statistics in Table 5.

Regardless of how the conformers are weighted or if just individual conformers are considered, the fit of  $\delta_{\text{C}}$  for **6** with predicted data for **6** is better than the mismatch with  $\delta_{\text{pred}}$  for **7**. For example, the match of  $\delta_{\text{C}}$  for **6** with  $\delta_{\text{pred}}$  for the (**6a** + **6b**)/2 average gives a  $|\Delta\delta|_{\text{av}}$  of 1.3 ppm and rms error of 0.5 ppm in the linear correlation, compared with 1.9 and 2.4 ppm, respectively, for the mismatch with  $\delta_{\text{pred}}$  for (**7a** + **7b**)/2. Likewise, any choice of  $\delta_{\text{pred}}$  for **7** fits better with  $\delta_{\text{C}}$  for **7** than do  $\delta_{\text{pred}}$  for **6**. The statistical analyses are given in Table 5. Thus, the scaled GIAO calculations at the B3LYP/3-21G(X,6-31+G\*)//MM3 level would be able to correctly permit an assignment of relative configuration for the 2-norbornanols even if experimental  $\delta_{\text{C}}$  for only one of the isomers were available.

The sesquiterpenes vulgarin, **8**, and epivulgarin, **9**, differ in configuration at C4. There was some confusion about relative configurations when a sample of **8** isolated from a natural source was assigned as **9** because the  $^{13}\text{C}$  shifts were very similar to those reported earlier<sup>37</sup> for **8** but differed noticeably at C14.<sup>38</sup> The difference was later shown to be an error in the initial report of  $\delta_{\text{C}}$  for C14, and the relative configurations were clearly established through comparative NOE studies of **8** and **9**.<sup>39</sup> As shown in Table 8, just two of the 15  $^{13}\text{C}$  signals differ between **8** and **9** by more than 2.0 ppm: 7.9 ppm at C15 and 3.7 ppm at C5.



Since the uncertainty about the identity of **8** and **9** arose from consideration of  $^{13}\text{C}$  shifts, it is interesting to see if computed  $^{13}\text{C}$  shifts could have resolved the question. MM3 calculations

(37) Ando, M.; Tajima, K.; Takase, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2737.

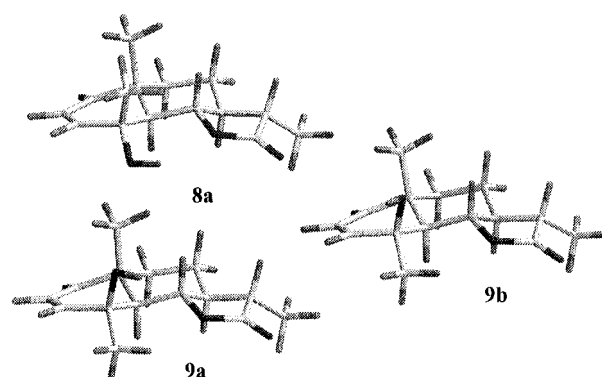
(38) Villar, A.; Zafra-Polo, M. C.; Nicoletti, M.; Galeffi, C. *Phytochemistry* **1983**, *22*, 777.

(39) Metwally, M. A.; Jakupovic, J.; Youns, M. I.; Bohlmann, F. *Phytochemistry* **1985**, *24*, 1103.

**Table 8.** Experimental<sup>a</sup>  $\delta_{\text{C}}$  for **8** and **9** and Predicted<sup>b</sup>  $^{13}\text{C}$  Chemical Shifts for Conformers **8a**, **9a**,<sup>c</sup> and **9b**<sup>d</sup>

	<b>8a</b> , $\delta_{\text{pred}}$	<b>8</b> , $\delta_{\text{C}}$	( <b>9a</b> + <b>9b</b> )/2 <sup>d</sup> $\delta_{\text{pred}}$	<b>9</b> , $\delta_{\text{C}}$
C1	200.5	201.6	203.8	203.1
C2	130.5	125.7	131.3	125.3
C3	156.0	151.7	152.1	150.2
C4	70.5	70.1	67.8	68.2
C5	55.7	54.7	52.1	51.0
C6	79.5	79.6	78.2	79.2
C7	53.0	52.5	53.4	52.3
C8	24.9	22.7	25.1	22.8
C9	35.7	34.3	34.3	32.5
C10	45.6	46.2	47.0	45.9
C11	39.5	40.6	39.8	40.1
C12	178.6	178.1	179.3	179.0
C13	14.3	12.4	14.4	12.5
C14	21.1	19.7	22.9	20.6
C15	24.1	23.8	30.6	31.7

<sup>a</sup> Reference 39. <sup>b</sup> From eq 2 and GIAO B3LYP/3-21G(X,6-31+G\*)//MM3 calculations. <sup>c</sup> Predicted shifts for individual conformers are given in the Supporting Information. <sup>d</sup> Average of **9a** and **9b** values.

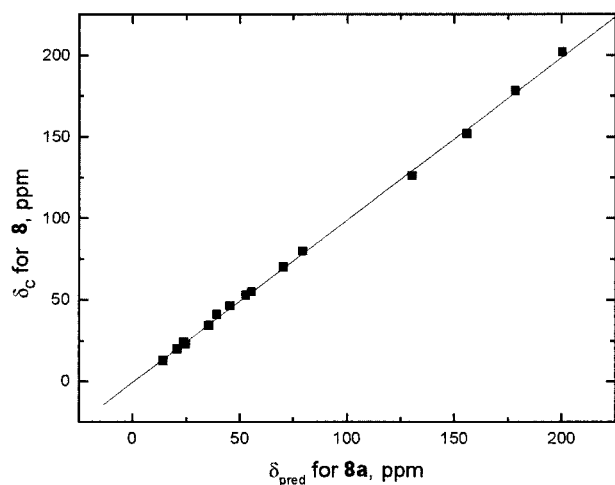


**Figure 3.** MM3-predicted geometries for the most stable conformers of **8** and **9**.

indicate that only a single conformer, **8a**, would contribute significantly in the case of **8**. Of the possible hydroxyl rotamers of **8**, **8a** is lower in energy than the other two because of hydrogen bonding to the oxygen in the ester linkage as shown in Figure 3. For **9**, MM3 predicts that the two hydroxyl rotamers, **9a** and **9b**, pictured in Figure 3 will contribute about equally. The  $\delta_{\text{pred}}$  are listed in Table 8 along with  $\delta_{\text{C}}$  for **8** and **9**. The C2 alkene position is not predicted well and gives the largest errors in the matches of  $\delta_{\text{C}}$  for **8** with  $\delta_{\text{pred}}$  for **8a**, and  $\delta_{\text{C}}$  for **9** with  $\delta_{\text{pred}}$  for **9a** or **9b** or the average of **9a** and **9b**. In the mismatches listed for **8** and **9**, the C15 methyl gives the largest errors of 6.8 and 7.6 ppm; these poor fits for an alkyl carbon are clear indicators the mismatches are not correct assignments of configuration.

The summary statistics comparing  $\delta_{\text{C}}$  for **8** and **9** to  $\delta_{\text{pred}}$  are given in Table 5. These also clearly indicate the correct configurational assignments. The rms error for the correlation of  $\delta_{\text{C}}$  for **8** with  $\delta_{\text{pred}}$  for **8a** is 1.8 ppm while the mismatch with the average of **9a** and **9b** yields an rms error of 2.7 ppm. The match of **9** with the average of **9a** and **9b** gives an rms error of 1.8 vs 3.4 ppm for the mismatch with **8a**. To illustrate the high quality of the predictions in the correct matches, Figure 4 shows the plot of  $\delta_{\text{C}}$  vs  $\delta_{\text{pred}}$  for the match of  $\delta_{\text{C}}$  for **8** with  $\delta_{\text{pred}}$  for **8a**. The proper sequence is predicted for all signals. It is obvious that the calculations could be a useful aid in signal assignment in cases where the structure is known.

The final example deals with the conformation of the amino steroid, 3 $\alpha$ -hydroxy-2 $\beta$ -(4-morpholinyl)-5 $\alpha$ H-androstan-17-one, **10**.<sup>40</sup> This example is the most subtle problem of the examples chosen for this paper and it illustrates both the limitations



**Figure 4.** Plot of experimental  $^{13}\text{C}$  shifts for **8** vs  $^{13}\text{C}$  shifts predicted for conformer **8a** through scaling of GIAO B3LYP/3-21G(6-31+G\*)/MM3 isotropic shieldings in eq 2.

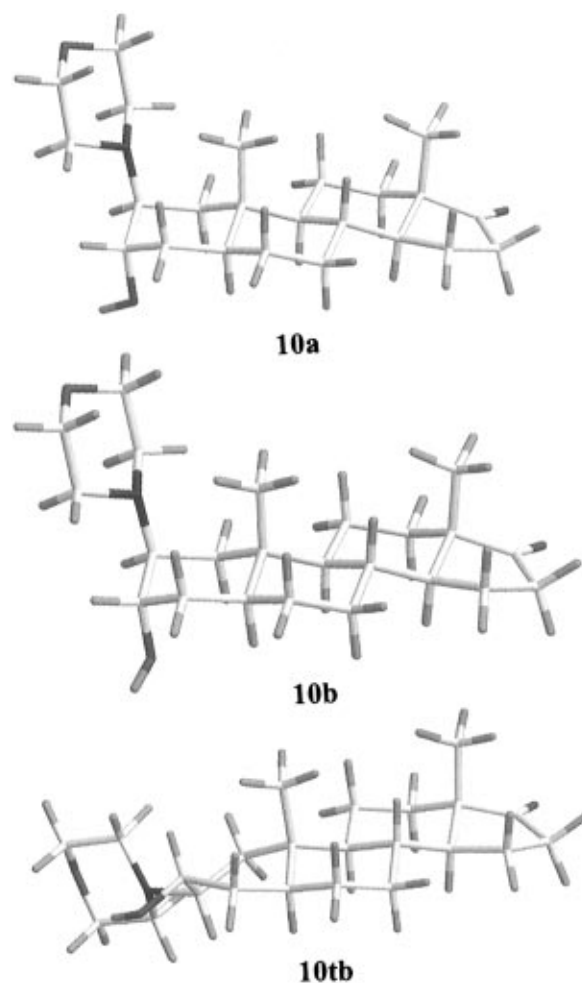
**Table 9.** Experimental<sup>a</sup>  $\delta_{\text{C}}$  for **10**(DMSO- $d_6$ ) and **10**( $\text{CDCl}_3$ ) and Predicted<sup>b</sup>  $^{13}\text{C}$  Chemical Shifts for Chair Conformers **10a** and **10b**<sup>c</sup> and Twist-Boat Conformer **10tb**

	$(10\text{a} + 10\text{b})/2^d$ $\delta_{\text{pred}}$	<b>10</b> (DMSO) $\delta_{\text{C}}$	<b>10tb</b> $\delta_{\text{pred}}$	<b>10</b> ( $\text{CDCl}_3$ ) $\delta_{\text{C}}$
C1	32.0	32.0	30.2	32.5
C2	65.8	66.0	64.6	65.0
C3	67.0	63.7	64.4	63.6
C4	34.3	32.1	36.9	34.1
C5	39.3	39.1	37.8	38.5
C6	28.8	27.4	29.5	27.9
C7	31.6	30.7	30.1	30.4
C8	35.7	34.1	36.3	34.9
C9	54.2	54.7	56.3	55.9
C10	37.5	36.1	36.2	35.9
C11	22.2	19.9	22.7	20.5
C12	33.4	31.5	33.5	31.5
C13	49.0	47.2	48.9	47.8
C14	50.8	50.8	50.7	51.2
C15	24.6	21.4	24.6	21.6
C16	37.5	35.4	37.4	35.7
C17	220.8	219.3	220.5	221.1
C18	14.5	13.5	14.4	13.8
C19	14.7	12.5	18.4	16.5
C20	51.2	51.7	47.8	49.0
C21	67.9	66.6	68.5	67.4

<sup>a</sup> Reference 40. <sup>b</sup> From eq 2 and GIAO B3LYP/3-21G(X,6-31+G\*)/MM3 calculations. <sup>c</sup> Predicted shifts for individual conformers are given in the Supporting Information. <sup>d</sup> Average of **10a** and **10b** values.

imposed by the accuracy of the computed shifts and the power of our computationally efficient approach to deal with large systems. A 600 MHz  $^1\text{H}$  NMR study concluded, principally via coupling constants, that ring A adopts a chair conformation in DMSO- $d_6$  and predominantly a twist-boat conformation (>90%) in  $\text{CDCl}_3$ .<sup>40</sup> The  $^{13}\text{C}$  chemical shifts, listed in Table 9, were also completely assigned in the same study. The largest difference in  $\delta_{\text{C}}$  between the two sets of data is 4.0 ppm at the C19 methyl. The average position for the two methylenes adjacent to nitrogen in the morpholine ring differs by 2.7 ppm, and C4 differs by 2.0 ppm. The difference of 1.8 ppm for the ring D carbonyl signal is typical of changes in ketone shifts with solvent and probably does not reflect any influence of the ring A conformation. All other changes are  $\leq 1.2$  ppm.

Two chair conformers that differ in rotation about the C3–OH bond, **10a** and **10b**, and one twist-boat conformer, **10tb**, are found to be isoenergetic within 0.2 kcal/mol in MM3



**Figure 5.** MM3-predicted geometries for the most stable conformers of **10**.

calculations. The twist-boat conformer has hydrogen bonding between the hydroxyl and the morpholine nitrogen. These conformers are shown in Figure 5. The scaled  $\delta_{\text{pred}}$  from B3LYP/3-21G(X,6-31+G\*)/MM3 GIAO calculations agree very well with experiment. The averaged **10a** and **10b**  $\delta_{\text{pred}}$  values deviate from **10**(DMSO)  $\delta_{\text{C}}$  by small amounts as seen in Table 5:  $|\Delta\delta|_{\text{av}}$  is 1.4 ppm and the maximum  $|\Delta\delta|$  is 3.2 ppm. The rms error for the  $\delta_{\text{C}}$  vs  $\delta_{\text{pred}}$  correlation is 1.1 ppm. In contrast, the comparison of **10**(DMSO)  $\delta_{\text{C}}$  with **10tb**  $\delta_{\text{pred}}$  produces a maximum  $|\Delta\delta|$  of 5.9 ppm at the C19 methyl, indicating a poor fit. The matchup of **10**(DMSO) with **10tb** also has a larger  $|\Delta\delta|_{\text{av}}$  of 2.0 ppm, and the rms error of 2.3 ppm is double that found for the match with the average of **10a** and **10b**. Thus, the ring A conformation of **10** in DMSO- $d_6$  can be identified as the chair from the  $^{13}\text{C}$  chemical shifts.

Unfortunately, the **10**( $\text{CDCl}_3$ )  $\delta_{\text{C}}$  data match equally well (rms error 1.3 ppm in the linear correlations) with  $\delta_{\text{pred}}$  for chair and twist-boat conformers as shown in Table 5. Perhaps the conformational equilibrium does not so predominantly favor the twist-boat conformer as previously concluded.<sup>40</sup> More likely, it may be stretching the limits of the accuracy of the computed shifts too far to distinguish between chair and twist-boat conformers in different media when the largest shift hydrogen predicted shift difference is 3.7 ppm and the largest observed difference is 4.0 ppm (both at C19). Nevertheless, the calculations are useful even if they could not be used directly to identify the conformer in  $\text{CDCl}_3$ . In comparing the chair to the twist-boat, the  $^{13}\text{C}$  shift is predicted to differ by  $\geq 0.5$  ppm at 14

positions, and at 13 of these the direction of the change in shift is the same as the observed change.

## Conclusions

Isotropic  $^{13}\text{C}$  NMR shieldings from GIAO calculations account well for relative chemical shifts even with relatively modest basis sets, as long as the effects of electron correlation are included via the DFT approach. However, the GIAO shieldings for the basis sets examined in this paper require empirical scaling to give good numerical agreement with experimental chemical shifts. After scaling, we find that B3LYP/3-21G calculations give statistically just as good agreement as B3LYP/6-31G\* calculations with our reference set of experimental  $^{13}\text{C}$  shifts when the same MM3 geometries are used.

In our strategy of using a small basis set for GIAO calculations along with molecular mechanics calculations to achieve maximum practicality, the best results are obtained in B3LYP/3-21G(X,6-31+G\*)/MM3 calculations, where the 3-21G basis set is augmented at heteroatoms with polarization and diffuse functions. The empirically scaled, predicted  $^{13}\text{C}$  shifts give good agreement (rms error  $\sim 3$  ppm) for a variety of organic structures containing C, H, O, and N. In carbonyl compounds where hydrogen bonding is involved, namely carboxylic acids and primary amides, the hydrogen bonding needs to be included in the geometry optimizations. This strategy also works well enough that computed  $^{13}\text{C}$  shifts can be used in comparison with experiment to identify conformations or relative stereochemistries.

MM3 molecular mechanics calculations can be used to provide the geometries for many common types of organic molecules, with an enormous increase in computational speed over molecular orbital geometry optimizations, but with some loss of quality in subsequent chemical shift predictions compared

to optimizations at the B3LYP/6-31G\* ab initio level. The molecular mechanics approach will not work well for molecules such as carbocations, where chemical shifts can be very sensitive to the extent of  $\sigma$ -bridging and where high-level ab initio calculations with correlation included are needed to describe the bonding and reach the appropriate geometry.<sup>41</sup> The approach has worked well on examples with saturated hydrocarbon frameworks having no more than a single heteroatom-containing (O and N) substituent per carbon position. The appropriateness of molecular mechanics geometry optimizations and the success of the GIAO DFT shielding calculations should be tested carefully for all other structural types. The demands on the accuracy of computed shifts are high for the purpose of addressing stereochemical issues, such that to be reliable, any prediction must give agreement within at least  $\leq 5$  ppm for all individual alkyl carbons, an overall mean deviation of about  $\leq 2.5$  ppm, and an rms error of  $\leq 2.0$  ppm for a correlation between  $\delta_{\text{C}}$  and  $\delta_{\text{pred}}$ .

**Note Added in Proof.** Two additional papers demonstrating the utility of computed  $^{13}\text{C}$  shifts for conformational assignments in solution have appeared since this paper was submitted.<sup>42,43</sup> One of these papers makes use of MM3 calculations and empirical corrections to computed shifts.<sup>43</sup>

**Supporting Information Available:** A listing of predicted  $^{13}\text{C}$  shifts for individual conformers **9a**, **9b**, **10a**, and **10b** (1 page). See any current masthead page for ordering and Internet access instructions.

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