Conformation and Configuration of Tertiary Amines via GIAO-Derived ^{13}C NMR Chemical Shifts and a Multiple Independent Variable Regression Analysis

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The ^{13}C chemical shifts of six tertiary amines of unambiguous conformational structure are compared to predicted ^{13}C NMR chemical shifts obtained via empirically scaled GIAO shieldings for geometries from MM3 molecular mechanics calculations. An average deviation, $|\Delta\delta|_{av}$, of 0.8 ppm and a maximum deviation, $|\Delta\delta|_{max}$, of 2.8 ppm between predicted and experimental ^{13}C shifts of the six tertiary amines of unambiguous structure are found. In several cases of tertiary amines subject to rapid exchange, where experimental ^{13}C shifts at room temperature are weighted averages of multiple conformers, a comparison of calculated ^{13}C shifts of all reasonable MM3 predicted conformers with experimental ^{13}C shifts via a multiple independent variable regression analysis provides an efficient method of determining the major and minor conformers. The examples presented are 2-methyl-2-azabicyclo[2.2.1]heptane and 1,6-diazabicyclo[4.3.1]decane, which each have two expected contributing structures, and 2-(diethylamino)propane and 1,8-diazabicyclo[6.3.1]-dodecane, where ten and seven low-energy conformers, respectively, are predicted by MM3 calculations.

Introduction

Theoretically computed ^{13}C chemical shifts can be obtained at a level of accuracy sufficient to allow application to configurational and conformational determination of organic molecules.[1] Many studies rely on high-level ab initio molecular orbital calculations for both geometry optimizations and shielding calculations in order to obtain reasonably accurate predictions of ^{13}C shifts.[2] Some of these include conformational studies of amides[3] and peptides.[4] Recently, we demonstrated that accurate (rms $\sim$ 3 ppm) predictions of ^{13}C chemical shifts for a variety of organic molecules containing C, H, O, and N could be achieved through empirical scaling of shieldings calculated from gauge including atomic orbitals (GIAO) theory with a small basis set and with geometries obtained from a computationally inexpensive molecular mechanics method.[5] The ^{13}C shifts obtained from MM3[6] geometries with GIAO calculations[7] carried out at the B3LYP/3-21G level augmented at the 6-31+G* level for heteroatoms allowed proper distinction among configurational and conformational possibilities for several organic molecules. Specifically, examples of the (*E*)- and (*Z*)-2-butenes, axial and equatorial methylcyclohexanes, *exo*- and *endo*-2-norbornanols, vulgarin and epivulgarin,[5] *trans*-cyclododecene,[1c] cyclohexene oxide,[1e] and sambutoxin[8] and conformational studies on 17-phenylvinyl-substituted estradiols[9] showed that the method is adequate for addressing questions of the conformation and relative stereochemistry of certain types of organic molecules.

In this paper, we examine whether or not GIAO calculations of ^{13}C shifts based on molecular mechanics geometries, when combined with a statistical analysis, can provide structural information regarding systems undergoing rapid exchange. In particular, we focus on tertiary amines because the numerous and extensive

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previous NMR studies of the dynamics and structure of tertiary amines provide a fertile testing ground.[10] Most of the previous studies[10b−e] relied on ^{1}H−^{1}H NOE measurements, or, more often,[10h,i] empirically established trends in ^{1}H and ^{13}C shifts to identify conformers detected in low-temperature experiments. Molecular mechanics calculations were often used to provide insight into possible structures and their relative energy content.[10h,i] In our approach, the molecular mechanics calculations are linked more directly to the NMR results by subsequent GIAO calculations of chemical shifts.[5] In cases of tertiary amines undergoing rapid conformational exchange, wherein ^{13}C resonances represent averages of multiple conformational states, the method described herein provides a means of identifying contributing conformers among a set of competing conformers.

Configuration and Conformation from ^{13}C Chemical Shifts. Most of the current applications of ^{13}C shifts to conformational or configurational questions arise from the γ-substituent effect.[11] A carbon under consideration, Cα, will be more shielded when a substituent attached at a γ-position is oriented in a syn or gauche alignment than when the alignment is anti. For a Cα−Cβ−Cγ−X or Cα−Cβ−Nγ−X fragment, where X = CH_3, OH, NH_2, Cl, or Br, a strong dependence on dihedral angle occurs such that the γ-effect is from about −10 to −5 ppm for dihedral angles of 0−60°, from −5 to −2 ppm for angles between 60 and 120°, and from about −2 to +2 ppm for angles between 60 and 180°.[11b] Certainly, empirical knowledge of the γ-substituent effect may allow pairs of conformers or stereoisomers to be distinguished without recourse to theoretical shielding calculations, although such calculations could substitute for the empirical generalization. However, in a practical question of stereochemistry or conformation, NMR data for only a single conformation or stereoisomer may be available, precluding direct comparison, and an appropriate library of data on model structures may also be unavailable. Furthermore, observed ^{13}C chemical shifts, δ_C, are often time-averaged values from weighted averages of contributing conformers, thereby making qualitative decisions of stereochemistry and conformation on the basis of empirical knowledge of the γ-substituent effect even more challenging. These are situations where accurately computed ^{13}C shifts and a statistical treatment of ^{13}C shifts based on predicted ^{13}C shifts for possible structures could be of practical value.

Table 1. Experimental[a] and Predicted[b] ^{13}C Chemical Shifts for 1, 2, 3, 4, 5, and 6

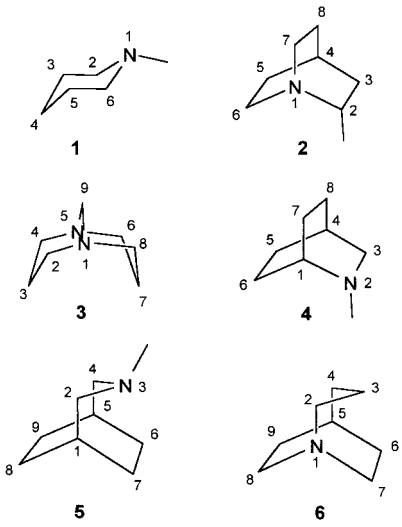
compd	carbon	δ_{pred}, ppm	expt δ_C, ppm	compd	carbon	δ_{pred}, ppm	expt δ_C, ppm
1	C2,6	54.3	54.4	**4**	C6	19.9	19.1
	C3,5	25.9	26.5		C7	27.3	30.1
	C4	24.2	23.9		C8	24.2	25.5
	CH_3	46.7	47.1		CH_3	42.5	42.5
2	C2	51.1	50.8	**5**	C1,5	29.9	30.4
	C3	35.1	34.1		C2,4	65.2	63.8
	C4	22.1	23.0		C6,7	23.5	24.6
	C5	26.9	26.8		C8,9	27.6	28.6
	C6	40.8	41.4		CH_3	46.3	46.9
	C7	49.7	50.8	**6**	C2	57.9	57.4
	C8	25.4	25.3		C3	25.6	25.7
	CH_3	21.0	22.1		C4	34.2	35.0
3	C2,4,6,8	50.9	50.5		C5	27.6	28.6
	C3,7	22.9	24.7		C6	25.7	24.7
	C9	69.5	68.0		C7	43.4	44.3
4	C1	51.1	49.4		C8	49.7	50.4
	C3	57.0	55.5		C9	30.7	30.3
	C4	26.0	25.4				
	C5	25.5	26.9				

[a] From ref 12. [b] From eq 1 and GIAO B3LYP/3-21G(N,6-31+G*)//MM3 calculations.

In the present paper, we take the approach of predicting ^{13}C shifts, δ_{pred}, for tertiary amines by scaling GIAO-calculated isotropic shieldings, σ. The appropriate scaling equation depends on the basis set. In this study, in which GIAO shielding calculations were obtained at the B3LYP/3-21G level with heteroatoms augmented at the 6-31+G* level, the appropriate scaling is given by eq 1, as determined previously.[5]

$$\delta_{pred} = -1.168\sigma + 230.2 \qquad (1)$$

A comparison of predicted ^{13}C shifts with observed chemical shifts for six cyclic tertiary amines of unambiguous structure, **1**−**6**,[12,13] illustrates the accuracy of the B3LYP/3-21G(N,6-31+G*)//MM3 GIAO calculations (Table 1). Experimental data for **4**−**6** were obtained at low temperature to freeze out rapid conformational exchange



in **5** and **6** and nitrogen inversion in **4**.[13] The average deviation, $|\Delta\delta|_{av}$, between observed and predicted shifts

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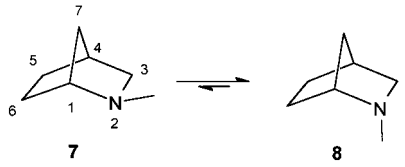
Table 2. Experimental[a] and Predicted[b] ^{13}C Chemical Shifts for 7 and 8

	7		8		7, 8
	δ_{pred}	δ_C[c]	δ_{pred}	δ_C[c]	δ_C[d]
C1	61.4	63.6	60.7	61.9	62.4
C3	60.5	62.1	58.7	59.4	60.9
C4	38.6	38.2	38.7	38.2	38.0
C5	29.3	27.5	30.9	30.3	28.3
C6	34.6	32.6	23.4	22.1	26.0
C7	31.3	31.4	40.2	38.7	35.5
CH_3	45.4	45.1	37.8	38.1	41.5

[a] From ref 13. [b] From eq 1 and GIAO B3LYP/3-21G(N,6-31+G*)//MM3 calculations. [c] At 126 K. [d] At room temperature.

for all six structures is 0.8 ppm. Additionally, the maximum deviation, $|\Delta\delta|_{max}$, between an observed and predicted shift in any of the six structures is 2.8 ppm. These results demonstrate that the calculations should be sufficiently accurate to define the stereochemistry of an unknown tertiary amine structure.

The endo and exo 2-methyl-2-azabicyclo[2.2.1]heptanes, **7** and **8**, respectively, serve as an example where GIAO B3LYP/3-21G(N,6-31+G*)//MM3 predictions are fully adequate to serve as the basis for a conformational or configurational assignment. Low-temperature studies revealed a 3:1 endo/exo ratio in solution at 126 K, and the ^{13}C chemical shifts of the endo and exo configurations were determined.[13] The endo and exo configurations were assigned by comparison of the pattern of differences in the ^{13}C shifts between the two structures to the analogous shift differences in endo and exo 2-methylbicyclo[2.2.1.]-heptanes.[14] The γ-substituent effect leads to shieldings of about 7 and 9 ppm at the methyl and C6, respectively, in **8** compared to those in **7**, but C1 and C3 shifts also differ by several parts per million between the two configurations. Similarly, the γ-substituent effect leads to a shielding of about 7 ppm of C7 in **7** compared to that in **8**. The δ_{pred} match the δ_C very well for both configurations (Table 2). The $|\Delta\delta|_{av}$ for individual shifts are 1.2 ppm for **7** and 0.7 ppm for **8**, and the maximum error for both is 2.2 ppm (Table 3). In contrast, the incorrect match of δ_C for **7** to δ_{pred} for **8** produces a $|\Delta\delta|_{av}$ of 5.3 ppm. The analogous mismatch for **8** gives a $|\Delta\delta|_{av}$ of 4.3 ppm. Clearly, the predicted ^{13}C shifts could have been used as the basis for the configurational assignment instead of the comparison with a model system, and this is indeed a more definitive approach.



7 **8**

In the example above, low-temperature ^{13}C data were available for the two separate isomers. For computed ^{13}C chemical shifts to be of broader practical use in conformational studies of tertiary amines and other compounds, they should be capable of distinguishing major and minor conformers in structures with time-averaged ^{13}C shifts due to high conformational mobility. To achieve this, we use here a statistical approach that treats all computed ^{13}C shifts of reasonable MM3-predicted conformers as independent variables in a multiple independent variable regression analysis[15] of the corresponding experimental ^{13}C data. Restraints included in the analysis require that each conformer in a given set of conformers be greater than or equal to 0% and that a conformer set is equal to 100% of the total population. In principle, the regression analysis then provides a quantitative weighting of the contributing structures in an equilibrium.

Table 3. Statistics for Conformer or Isomer Matches and Mismatches of Experimental[a] δ_C with δ_{pred} from B3LYP/3-21G(N,6-31+G*)//MM3 Calculations

δ_C	δ_{pred}	$\|\Delta\delta\|_{max}$	$\|\Delta\delta\|_{av}$
7	**7**	2.2	1.2
8	**8**	1.5	0.8
7	**8**	12.5	5.3
8	**7**	10.5	4.3
9	**9a**	12.1	6.0
9	**9b**	1.1	0.6
DEAP major (**GG′G′**)	**GG′G′**	3.7	1.8
	AGA	11.8	4.8
	GAG′	9.0	4.1
	GGG′2	8.0	4.3
	GGG′1	8.0	4.2
	AGG′	8.8	4.2
	AG′A	11.5	5.9
	GGA	11.6	6.0
	G′G′G′	7.5	4.0
	G′GG′	10.3	4.5
DEAP minor (**AGA**)	**GG′G′**	12.4	4.8
	AGA	2.8	1.6
	GAG′	4.5	2.6
	GGG′2	14.1	7.1
	GGG′1	13.3	6.2
	AGG′	7.2	3.7
	AG′A	8.3	4.0
	GGA	12.7	5.9
	G′G′G′	12.3	7.9
	G′GG′	12.3	7.2

In the case of **7** and **8**, using the δ_{pred} of each carbon of both isomers as independent variables and their room-temperature time-averaged δ_C as dependent variables, we find that the regression analysis correctly identifies the major configuration to be the endo structure with a 60% contribution and the minor configuration to be the exo structure with a 40% contribution (Table 4). While a 3:1 endo/exo ratio was found at low temperature, the temperature difference is expected to affect the conformational equilibrium.[16] The quality of the fit may also be affected by temperature-dependent changes in chemical shifts.[17,18] Performing a regression analysis that instead uses the experimentally determined low-temperature chemical shifts of both isomers as independent variables and the room-temperature time-averaged δ_C as dependent variables yields a similar 57% endo and a 43% exo contribution (Table 4).

In another approach to test the limitations of the population analysis, the low-temperature NMR data for the individual structures of **7** and **8** were subjected to

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Table 4. Summary of the Multiple Independent Variable Regression Analyses[a] of Averaged and Low-Temperature δ_C Using the Predicted ^{13}C Shifts of MM3 Structures

independent variables	dependent variables	structures	statistical population (%)	standard error (%)	exp population
δ_{exp}	δ_C				
7,[b] **8**[b]	**7**, **8**[c]	**7**	57	4	75[d]
		8	43	4	25[d]
δ_{pred}	δ_C				
7, **8**	**7**, **8**[c]	**7**	60	4	75[d]
		8	40	4	25[d]
7, **8**	**7**[b]	**7**	92	2	100
		8	8	3	0
7, **8**	**8**[b]	**7**	7	3	0
		8	93	3	100
9a, **9b**	**9**[c]	**9a**	5	3	n/a
		9b	95	2	n/a
all DEAP	DEAP[c]	**GG′G′**	73	20	75[d]
		AGA	10	9	25[d]
		GAG′	10	12	0
		GGG′2	0	3	0
		GGG′1	0	4	0
		AGG′	0	0	0
		AG′A	7	7	0
		GGA	0	1	0
		G′G′G′	0	1	0
		G′GG′	0	4	0

[a] Constraints: each conformer is greater than or equal to 0%. Conformer sets **7**−**8**, **9a**−**9b**, and **GG′G′**−**G′GG′** are equal to 100%. [b] Low-temperature experimental ^{13}C shifts.[13,21] [c] Averaged shifts at room temperature. [d] Low-temperature-determined populations. Statistical populations are derived from averaged δ_C at room temperature.

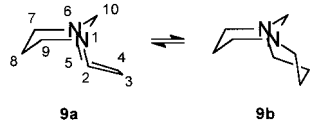
the regression analysis. In principle, the analysis should give 100% of **7** as the population in the analysis of data for **7** and, likewise, 100% of **8** in the analysis of data for **8**. Using the δ_{pred} of both configurations as independent variables and the low-temperature-determined ^{13}C chemical shifts of the exo configuration, **7**, as the dependent variables, we find that the statistical analysis correctly identifies the exo conformer, but gives 92% instead of 100% as the exo population (Table 4). The analogous analysis, which uses the determined endo ^{13}C chemical shifts as the dependent variables, yields the endo conformer as 93% of the population rather than 100%.

A thorough examination of the *out,out* to *out,in* transition for 1,(*n*+2)-diazobicyclo[*n*.3.1]alkanes by Alder, Weisman, et al. provides useful test cases for the purposes of the present study.[19] Their study used photoelectron, ^1H NMR, ^{13}C NMR, and IR spectra as well as force field and semiempirical MO calculations. In one of the systems examined, two conformers of 1,6-diazabicyclo[4.3.1]-decane, **9**, were determined by MM2[20] calculations to be similar in energy, with **9a** lower in energy than **9b** by 0.7 kcal/mol. Our recalculations of conformation in the MM3 method found the opposite order with **9b** being lower in energy by 1.9 kcal/mol. No experimental evidence was considered as providing any further insight into the conformational preference.[19] However, our regression analysis of the experimental δ_C, based on predicted ^{13}C chemical shifts of the two possible conformers **9a** and **9b**, clearly identifies the dominant conformer to be **9b** with a population of 95% (Table 4). In light of the model study of **7** and **8** above, it is likely that this result indicates that **9b** is the only type of conformation present.

Table 5. Experimental[a] ^{13}C Chemical Shifts for 9 and Predicted[b] Shifts for 9a and 9b

	9a	**9b**	**9**
	δ_{pred}	δ_{pred}	δ_C
C2,5	46.7	54.5	54.8
C3,4	23.0	30.7	30.6
C7,9	50.8	53.1	52.8
C8	9.3	22.5	21.4
C10	66.3	65.3	66.3

[a] From ref 19. [b] From eq 1 and GIAO B3LYP/3-21G(N,6-31+G*)//MM3 calculations.



9a **9b**

The calculated ^{13}C chemical shifts show significant differences between **9a** and **9b**. A simple, direct comparison of δ_{pred} and δ_C also clearly reveals that **9b** must be the correct conformer (Table 5), if only one conformer is present. The **9b** conformer would of course be rapidly equilibrating with its mirror image twist conformer to average the two sides, so the reported shifts for C2,5, C3,4, and C7,9 are averaged values. The $|\Delta\delta|_{av}$ from individual shifts in **9** are 6.0 ppm for **9a** and 0.6 ppm for **9b**, and the $|\Delta\delta|_{max}$ are 12.1 ppm for **9a** and 1.1 ppm for **9b** (Table 3); so, the δ_C for **9** clearly match better with the δ_{pred} for **9b**.

A more complex conformational problem with numerous possible conformations is presented by 2-(diethylamino)propane (DEAP), a molecule examined by Brown and Bushweller via low-temperature measurements and MM2 molecular mechanics calculations.[21] The low-temperature ^1H and ^{13}C study revealed, at 100 K, two conformers with a 3:1 ratio. The MM2 calculations found 10 possible conformers within 3.7 kcal/mol. Our recalculations of conformation in the MM3 method found these conformers all to be within 2.6 kcal/mol (Figure 1). After a rigorous analysis of established ^1H and ^{13}C chemical shift trends to identify the conformations, Brown and Bushweller concluded that DEAP at 100 K was 75% **GG′G′** and 25% **AGA** in their terminology.

The experimentally determined low-temperature ^{13}C shifts for **GG′G′** and **AGA** match quite well with our calculated ^{13}C shifts (Table 6) of predicted conformers **GG′G′** and **AGA** with $|\Delta\delta|_{av}$ of 1.8 and 1.6 ppm, respectively, and a $|\Delta\delta|_{max}$ of 3.7 ppm (Table 3). Predicted ^{13}C shifts of any of the other eight conformers did not match as well, each having a $|\Delta\delta|_{av}$ greater than 2.5 ppm in matches with the set of experimentally determined ^{13}C shifts for either the major or minor conformers (Table 3). Thus, in this case, the assignment of conformational structure could be based on calculated ^{13}C shifts rather than a detailed comparison with ^1H and ^{13}C shifts of model structures.

(19) Alder, R. W.; Heilbronner, E.; Honegger, E.; McEwen, A. B.; Moss, R.; Olefirowicz, E.; Petillo, P. A.; Sessions, R. B.; Weisman, G. R.; White, J. M.; Yang, Z. *J. Am. Chem. Soc.* **1993**, *115*, 6580.

(20) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) MM2-(77) Program: Allinger, N. L.; Yuh, Y. H. *QCPE* **1981**, *12*, 395. (c) Petillo, P. A.; Coolidge, M. B.; Weisman, G. R. *QCPE Bull.* **1985**, *5*, 68.

(21) Bushweller, C. H.; Brown, J. H. *J. Am. Chem. Soc.* **1995**, *117*, 12567.

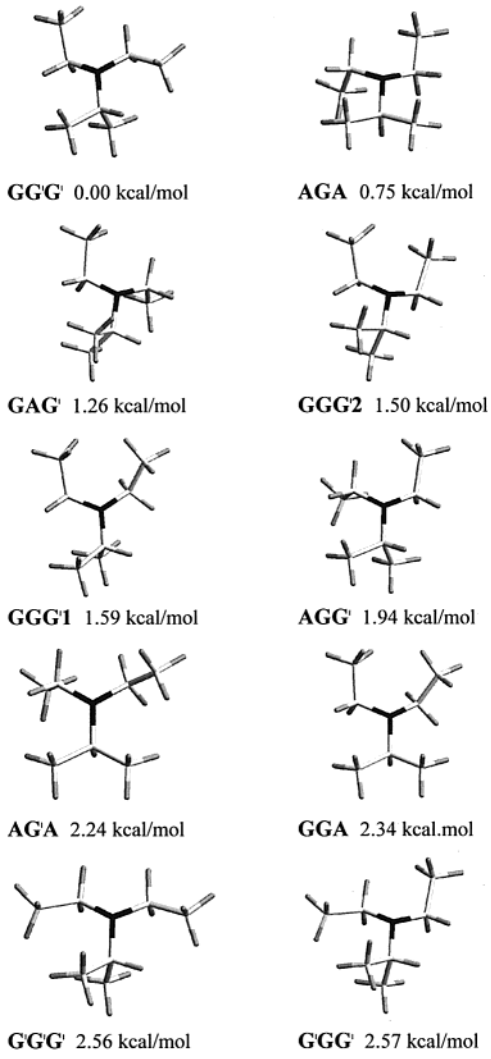


Figure 1. MM3-predicted conformers and relative steric energies of DEAP.

Table 6. Experimental[a] and Predicted[b] ^{13}C Chemical Shifts for DEAP

conformer	CH_3[c]	CH_2[c]	CH_3[d]	CH_2[d]	CH	CH_3[e]	CH_3
			δ_{pred}				
GG′G′	15.32	40.33	14.30	41.30	45.60	22.63	9.63
AGA	1.77	38.16	14.41	41.08	48.05	22.33	22.88
GAG′	14.51	34.96	7.87	45.97	53.62	23.10	20.12
GGG′2	20.85	41.33	17.93	52.37	55.84	23.60	11.62
GGG′1	17.11	41.15	20.05	51.25	55.90	22.72	14.23
AGG′	11.00	35.39	14.58	45.62	56.68	23.43	18.29
AG′A	6.20	47.79	19.80	49.71	49.56	24.50	22.60
GGA	16.50	48.05	20.40	48.68	55.15	22.72	24.29
G′G′G′	19.00	48.97	16.12	50.30	46.61	26.24	9.78
G′GG′	17.71	40.21	16.13	52.64	58.19	26.78	11.01
			exp δ_C				
averaged	13.35	43.64	13.35	43.64	49.92	18.44	18.44
major	13.91	41.49	12.72	44.99	47.85	21.86	11.13
minor	3.81	39.50	13.08	43.32	50.88	22.02	22.02

[a] From ref 21. [b] From eq 1 and GIAO B3LYP/3-21G(N,6-31+G*)//MM3 calculations. [c] For ethyl group at left in Figure 1 structures. [d] For ethyl group at right in Figure 1 structures. [e] From left or top methyl of *i*-propyl group in Figure 1 structures.

In an earlier paper on identifying conformation and configuration from ^{13}C shifts, we suggested that two of the criteria for judging a good quality match between δ_C and δ_{pred} should be that (1) individual deviations, $\Delta\delta$, are less than |5.0| ppm for alkyl carbons and (2) the $|\Delta\delta|_{av}$ are 2.5 ppm or less. For DEAP, the δ_C assignments in Table 6 for each type of alkyl group in the major and minor conformers were chosen so as to give the best match to the δ_{pred} for **GG′G′** and **AGA**. In comparisons with other conformers (Table 3), other signal assignment schemes were used so as to give the best possible match in each case; however, in no case did any of the other conformers produce a match that came close to meeting the criteria. In general, for all of the amines **1**−**9** plus DEAP where individual structures have been matched, the quality of the matches between δ_C and δ_{pred} easily meets the criteria. Figure 2 provides an overview of the range and quality of the fit in all of these systems. The largest $|\Delta\delta|_{max}$ is 3.7 ppm.

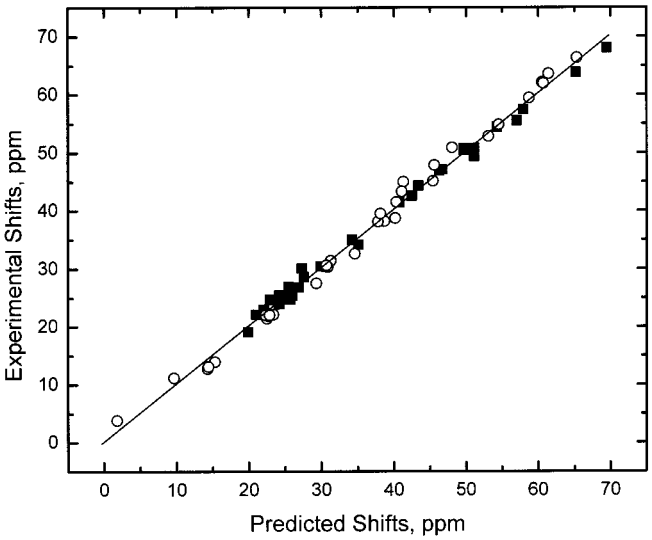


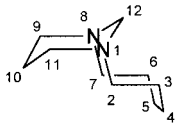
Figure 2. Plot of δ_C vs δ_{pred} for **1**−**9** and DEAP. Solid squares represent data from reference structures **1**−**6**; open circles are data from matches with individual structures **7**, **8**, **9b**, **GG′G′**, and **AGA**. The line is the ideal line with a slope of 1.0 and an intercept of 0.0.

The regression analysis of the averaged experimental ^{13}C shifts of DEAP at room temperature included the calculated ^{13}C shifts of all 10 conformers as sets of independent variables. The regression analysis finds the major conformer to be **GG′G′**, with 73% of the overall population (Table 4). The **AGA** conformer is also found to contribute as a minor conformer (10%), but the statistical analysis also finds two other conformers, **GAG′** (10%) and **AG′A** (7%), not observed at low temperature (Table 4). Although only the **GG′G′** and **AGA** conformers were expected, these results demonstrate the capability of the regression analysis based on predicted ^{13}C shifts in determining the major and minor conformer among 10 possibilities.

The regression analysis works well in the instance of DEAP because there are substantial differences in chemical shifts among the 10 conformers. As can be seen in Table 6, every carbon atom except one of the methyl carbons of the *i*-propyl group has a predicted range of shifts of at least 11 ppm among the conformers. There are some unique shifts, such as the δ_{pred} of 1.77 ppm for a methyl carbon in **AGA**, that aid in the success. Unique shifts arise in amines such as DEAP from γ-substituent interactions and lone pair effects. Clearly, for the regres-

sion analysis approach to be a generally useful tool, the conformations considered must at least have unique combinations of chemical shifts.

The final example comes from the study of Alder, Weisman, et al. and deals with the conformation of a bicyclic tertiary amine, 1,8-diazabicyclo[6.3.1]dodecane, **10**.[19] This example illustrates the usefulness of the computed ^{13}C shifts in analyzing ^{13}C data and in complementing other types of NMR data in a structural study. The analysis of ^{1}H chemical shifts, ^{1}H−^{1}H coupling constants, and variable-temperature ^{13}C experiments indicated a mixture of equatorial (eq)-axial (ax) and ax-ax conformers for **10**.[19] Low-temperature ^{13}C experiments performed at −12, −47, and −67 °C revealed that the chemical shift of the central carbon in the fragment in the six-membered ring, N−C−*C*−C−N, is strongly temperature dependent, suggesting that conformational biasing occurred as a function of temperature. The authors concluded that the eq-ax and ax-ax mixture shifted toward a significant increase in the ax-ax conformer, upon lowering the temperature.



10

Seven possible conformers for **10** were found through MM2 calculations: five eq-ax, **10a**−**e**, one ax-ax, **10f**, and one twist boat (tb)-eq-ax, **10g**, with relative energies within 1.4 kcal/mol (Figure 3).[19] The ax-ax conformer, **10f**, was 1.4 kcal/mol higher in energy than the five lowest-energy eq-ax conformers, **10a**−**e**, and 0.4 kcal/mol above the tb-eq-ax conformer, **10g**. Our recalculations of conformation in the MM3 method found these seven conformers to be within 3.56 kcal/mol and in a different relative order from that found by MM2 calculations (Figure 3). The MM2 calculations found the eq-ax conformer **10d** to be lower in energy than **10b** and **10c**. The most significant distinction between the MM2 results and our MM3 recalculations is that the MM3 force field finds the twist boat-eq-ax conformer **10g** to be higher in energy than the MM2-predicted highest-energy ax-ax conformer **10f** by 1.57 kcal/mol. The inconsistency may be a consequence of the MM2 inclusion of explicit lone pairs on the nitrogen atom. It is known that the MM2 inclusion of these lone pairs overestimates the energy cost of the flattening of a nitrogen atom, as would be expected to occur in the ax-ax conformer.[22]

Applying our regression analysis with the calculated ^{13}C shifts (Table 7) of all seven conformers, **10a**−**g**, to the experimentally determined ^{13}C shifts of **10** at various temperatures yields a result that supports the previous conclusion determined by the ^{1}H coupling and ^{13}C NMR study. At room temperature, a mixture of 76% eq-ax (34% **10a**, 26% **10b**, 10% **10c**, and 6% **10d**), 24% ax-ax (**10f**), and no tb-eq-ax (**10g**) is found by the regression analysis (Table 8). As the temperature is lowered to −12, −47, and −67 °C, the population of the ax-ax conformer (**10f**) increases sequentially to 41, 61, and 69%, while the total eq-ax population is reduced to 28% (24% **10a** and 4% **10d**). Thus, our regression analysis based on predicted ^{13}C shifts strongly supports the earlier conclusion of Alder, Weisman, et al. regarding the shift in population toward the ax-ax conformer at low temperatures, while also revealing that **10a** is the other major conformer at low temperature.

(22) Schmitz, L. R.; Allinger, N. L. *J. Am. Chem. Soc.* **1990**, *112*, 8307.

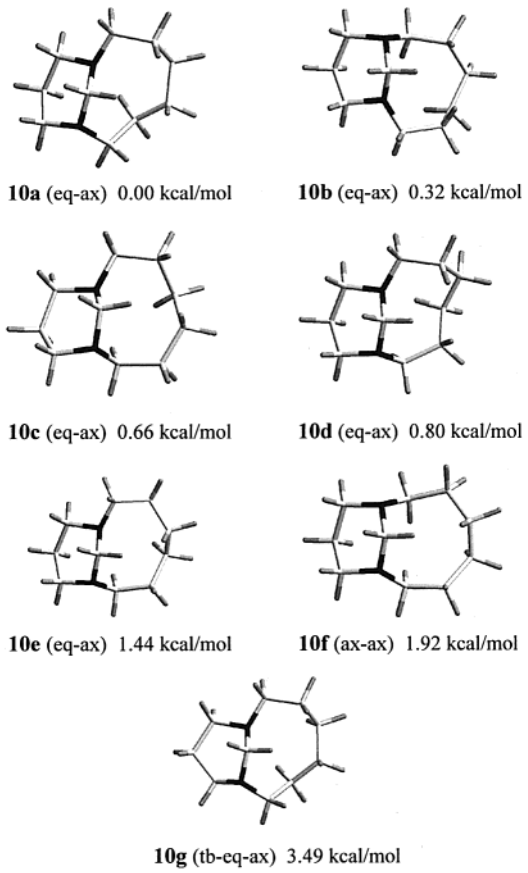


Figure 3. MM3-predicted conformers and relative steric energies of 1,8-diazabicyclo[6.3.1]dodecane.

Table 7. Experimental[a] and Predicted[b] ^{13}C Chemical Shifts for 10

	δ_C					
T (°C)	C2,7	C3,6	C4,5	C9,11	C10	C12
+29	53.15	28.77	28.54	53.44	19.37	66.18
−12	52.95	28.67	28.15	53.21	17.87	65.21
−47	52.88	28.70	27.82	52.98	16.15	64.19
−67	52.89	28.74	27.69	52.89	15.41	63.74

	δ_{pred}					
conformer	C2,7	C3,6	C4,5	C9,11	C10	C12
10a	56.88	32.81	33.66	54.80	24.53	66.24
10b	48.56	22.92	24.69	52.68	19.22	65.30
10c	48.65	30.53	26.32	53.72	19.82	68.66
10d	52.95	22.12	30.43	52.45	18.66	65.59
10e	54.50	32.18	32.83	52.35	19.05	72.89
10f	54.19	30.68	29.66	53.55	13.67	63.34
10g	51.83	23.62	29.13	42.94	17.06	59.01

[a] From ref 19. [b] From eq 1 and GIAO B3LYP/3-21G(N,6-31+G*)//MM3 calculations.

Conclusions

Predicted ^{13}C NMR chemical shifts from empirically scaled GIAO shieldings with small basis sets, polarization

Table 8. Multiple Independent Variable Regression Analyses[a] of the ^{13}C NMR Shifts of 10 at Various Temperatures Using Predicted ^{13}C Shifts of MM3 Structures

independent variables δ_{pred}	T (°C)	statistical population (%)	standard error (%)
10a	+29	34	6
	−12	30	5
	−47	27	5
	−67	24	5
10b	+29	26	9
	−12	16	7
	−47	6	3
	−67	0	1
10c	+29	10	6
	−12	4	4
	−47	0	1
	−67	0	1
10d	+29	6	9
	−12	6	7
	−47	6	6
	−67	4	4
10e	+29	0	4
	−12	0	2
	−47	0	2
	−67	0	2
10f	+29	24	13
	−12	41	10
	−47	61	4
	−67	69	4
10g	+29	0	1
	−12	3	1
	−47	0	2
	−67	3	2

[a] Constraints: Each conformer is greater than or equal to 0%. Conformer sets **10a**−**g** are equal to 100%.

and diffuse functions applied to nitrogen, and MM3 geometries provide a basis for identification of conformations and configurations of tertiary amines through comparison with experimental ^{13}C shifts. In the cases of tertiary amines subject to rapid conformational exchange examined here, a comparison of calculated ^{13}C shifts of all reasonable MM3-determined conformers with experimental ^{13}C shifts via a multiple independent variable regression analysis provides an efficient method of determining the major and minor conformers among a competing set of MM3-predicted conformers. While the regression analysis yields populations of conformers in a quantitative fashion, the results should probably be viewed in a more qualitative sense, i.e., as an indication of major and minor conformations. Lambert et al. have shown clearly that the measurement of population differences in equilibrating systems on the basis of ^{13}C shifts is not always reliable because of the inherent nonlinear temperature dependence of ^{13}C shifts for individual contributing structures.[17] The approach also does not accommodate solvent effects at present. Nonetheless, in cases where chemical shift differences among possible contributors are substantial, as in the case with several of the amines considered here, the regression analysis can provide a fair approximation of the conformational distribution. The application of this approach as a general tool will depend on the quality of the MM3 calculations and GIAO shielding calculations for particular structural types.

Supporting Information Available: MM3 steric energies and Cartesian coordinates for all conformers discussed; also, as an example, the GIAO shieldings from the Gaussian 98W calculation for **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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