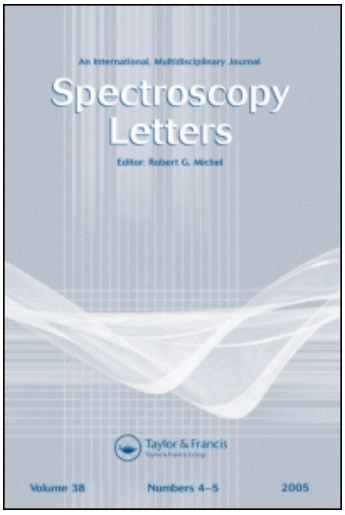

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Conformational Analysis of Longifolene

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ABSTRACT We describe the stable conformation of the tricyclic sesquiterpenoid, longifolene, by experimental NMR data and molecular mechanics calculations of the coupling constants. The flexible seven-membered ring of longifolene adopts a twist-chair conformation. Analysis of the coupling constants, particularly of the methylene protons in the cycloheptane ring moiety, agrees with this low-energy conformation. Low-temperature NMR experiments and nuclear Overhauser effect measurements indicate that there is a single exchange-averaged NMR spectrum that has the highest population of the most stable conformer.

KEYWORDS conformational analysis, longifolene, NMR, spectral simulation

INTRODUCTION

The intriguing chemical structure of longifolene **1** (Fig. 1), a tricyclic sesquiterpenoid natural product, has received much synthetic attention for four decades.[1–15] The structure of longifolene was revealed by x-ray crystallography,[16–19] and its solution conformation appeared to be the same.[20] As part of our interest in the syntheses of tricyclic natural products, we developed an efficient synthesis to the penultimate precursor of longifolene **2** (Fig. 1) and assigned its ^{1}H and ^{13}C chemical shifts using 1D and 2D NMR techniques.[14]

Recently, we reported the stereospecific assignments of the ^{1}H and ^{13}C chemical shifts for longifolene **1** by *ab initio* calculations using a RHF/6-311G* basis set.[21] These calculations gave rise to the proposal that there are two low-energy conformations **1A** and **1B**, with a difference of 1.39 kcal in favor of **1A** (Fig. 2). The calculated chemical shifts for the low-energy conformation **1A** agreed more closely with the experimental value. Major differences in the calculated chemical shifts were found for the H4a, H4b, H6a, and H6b protons. These protons appear in different positions in the two conformations with respect to the exocyclic double bond.

The 1.39 kcal/mol energy difference between the two conformations translates to a 10:1 equilibrium ratio at 298 K. Therefore, lowering the temperature is expected to increase the ratio of the low-energy conformation **1A** relative to **1B** and affect the chemical shifts of the H4a, H4b, H6a, and H6b protons of longifolene. A higher concentration of one conformer and a lower tumbling rate at lower temperatures would enhance the detection of the nuclear Overhauser effect. In this article, we study the

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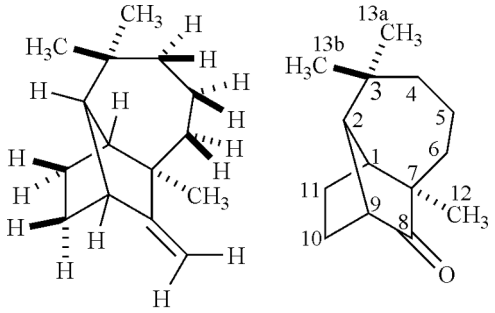

FIGURE 1 **Structures of longifolene 1 and its precursor 2. The H atoms indicated by bold lines are referred as H_b's and those with dashed lines are H_a's.**

conformation of longifolene by NMR experiments at low temperatures. To support the experimental studies, coupling constants for the two conformations **1A** and **1B** were calculated by *ab initio* calculations,[22] and simulations were performed by the gNMR program.[23]

MATERIALS AND METHODS

NMR Experiments

NMR samples were prepared from commercially available longifolene (purchased from Sigma-Aldrich) by dissolving 100 mg in 0.6 mL $CDCl_3$ or C_6D_6. The NMR experiments were recorded on a Bruker Biospin Avance 400-MHz NMR spectrometer using standard pulse sequences and parameters for one-dimensional proton, carbon, DEPT 45, and DEPT 135 experiments. The temperature of the sample was maintained at 22°C using compressed air. For various low-temperature experiments, the temperature was maintained by switching the air supply to evaporating liquid nitrogen (T.W. Smith Corp., New York, NY, USA).

The two-dimensional homonuclear COSY spectrum was recorded in magnitude mode with a sweepwidth of 5.4 ppm, 1024 complex data points, and 8 transients for each Free Induction Decay (FID), in t2. The data were processed with an unshifted sine bell in both dimensions. The two-dimensional heteronuclear COSY spectra were recorded with direct ^{13}C detection and broadband Waltz decoupling with a 5.4 ppm sweepwidth in the ^{1}H dimension and 110 ppm sweepwidth in the ^{13}C dimension, 64 transients, and 2048 complex points for each FID in t2. The data were processed with an unshifted sine bell in both dimensions.

The two-dimensional NOESY spectrum was recorded in States-TPPI mode with a spectral width of 5.4 ppm with 24 transients for each FID and 2048 complex data points in t2. A 180° phase-shifted square sine bell function was applied in both dimensions. The NOESY spectrum was run at 22°C and 0°C with mixing times of 400 ms, 500 ms, and 600 ms.

Coupling Constant Calculations

The two conformations of longifolene, **1A** and **1B,** identified as low-energy conformations in our earlier work,[21] served as starting conformations for calculating the coupling constants between various nuclei. Calculations of the chemical shifts and coupling constants were carried out by the Guassian program[22] on a desktop computer using a RHF/6-311G* basis set without solvent.

Spectral Simulation

The spectral frequency was set to 400.13 MHz, linewidth to 1.5 Hz, and the spectrum was processed with a line broadening of 0.3 Hz. The one-dimensional proton NMR spectra for the two conformations of longifolene, **1A** and **1B**, were simulated by the gNMR program[23] using the clearly observable experimental chemical shift data. However, in the dense spectral region of 0.80–1.7 ppm, experimental coupling constants could not be measured because of overlap. Therefore, these coupling constants were adjusted until the simulated spectrum of longifolene appeared to closely match the experimental NMR spectrum.

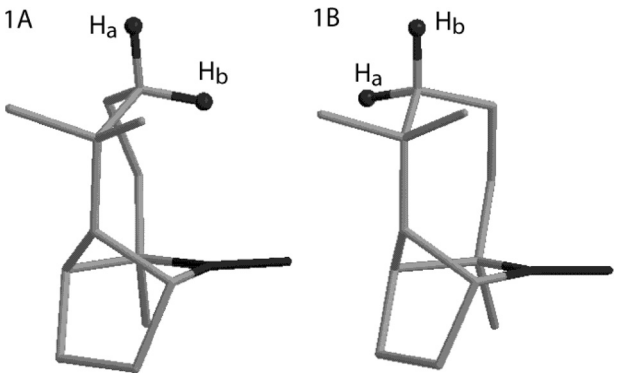

FIGURE 2 **Stick drawing of the two low-energy conformations of longifolene: 1A is 1.39 kcal lower in energy than 1B.**

RESULTS AND DISCUSSIONS

Effect of Temperature and Solvent on the Conformation

The proton NMR spectra of longifolene in $CDCl_3$ at various temperatures from −45°C to +45°C are shown in Fig. 3. There seems to be no temperature dependence in this range, consistent with a low-energy barrier of approximately 10 kcal/mol according to the calculations[22] between conformations **1A** and **1B**.[24] Complete stereospecific assignments of the protons were carried out using DEPT 135, COSY, HETCOR, and NOESY experiments, and the chemical shifts are listed in Table 1. Note that H4a is calculated to be at 0.88 ppm in conformation **1A** and at 1.32 ppm in conformation **1B** and the H4b is calculated to be at 1.62 ppm in conformation **1A** and at 1.02 in conformation **1B**. The comparison of these data to the experimental value supports a larger population of conformation **1A** with a ratio of **1A** and **1B** to be 10:1 at 298 K. Lowering the temperature to 273 K would increase the ratio to 13:1. Although one could expect the temperature differential to affect the chemical shifts of the H4a and H4b protons, there is little change. Similarly, no difference is observed experimentally for the H6a and H6b. The variable temperature NMR experiments indicate that due to rapid interconversion between **1A** and **1B**, we only observe a single exchange-averaged NMR spectrum. The minor noticeable changes in the appearance of the proton NMR spectra in Fig. 3 are due to line broadening and minor changes in the mole fraction of the conformers as a result of lowering the temperature. Assignment of ^{1}H and ^{13}C chemical shifts at −45°C by 2D NMR experiments showed that the chemical shift differences compared with room temperature were only 0.0–0.5 ppm for carbons and 0.00–0.05 ppm for protons. This is consistent with the predominant presence of conformation **1A** in this temperature range.

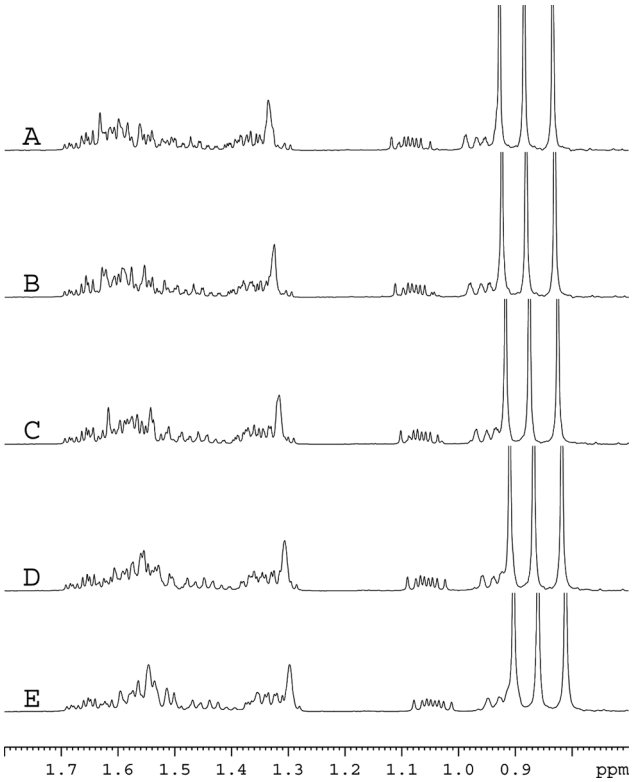

FIGURE 3 **Proton NMR spectra of longifolene at various temperatures: A, B, C, D, and E as marked on the spectra correspond with temperatures of +45, +25, 0, −25, and −45°C, respectively.**

Table 1 **Proton NMR Chemical Shifts of Longifolene in C_6D_6 and $CDCl_3$ at 22°C. All Proton Chemical Shifts are Referenced to TMS. The Calculated Chemical Shifts of the Two Conformations are Shown for Comparison**

	Solvent C_6D_6 (Experimental)	Solvent $CDCl_3$ (Experimental)	Conformation **1A** (Calculated)	Conformation **1B** (Calculated)
H1	1.98	2.00	1.81	1.71
H2	1.37	1.32	1.00	1.10
H4 (a, b)	1.08, 1.81	0.96, 1.59	0.88, 1.62	1.32, 1.02
H5 (a, b)	1.76, 1.49	1.53, 1.38	1.45, 1.31	1.19, 1.52
H6 (a, b)	1.58, 1.75	1.53, 1.63	1.46, 1.63	1.36, 1.45
H9	2.59	2.55	2.42	2.42
H10 (a, b)	1.25, 1.70	1.08, 1.67	1.17, 1.58	1.17, 1.55
H11 (a, b)	1.67, 1.38	1.58, 1.35	1.50, 1.34	1.52, 1.31
H12	0.97	0.84	1.01	1.09
H13 (a, b)	1.05, 1.00	0.92, 0.88	0.96, 0.92	0.97, 0.94
H14 (a, b)	4.64, 4.88	4.46, 4.72	4.65, 5.00	4.58, 5.07

We also studied the solvent effect on the conformation of longifolene by carrying out the NMR experiments in C_6D_6. Table 1 lists the stereospecifically assigned chemical shifts using various 1D and 2D NMR experiments. In C_6D_6, the entire molecule experienced a deshielding effect compared with $CDCl_3$. We examined the changes at H4a, H4b, H6a, and H6b and found no evidence for a conformational change due to solvent polarity.

Coupling Constant Analysis

To further support our assignment of the stable conformation of longifolene, the coupling constants for conformations **1A** and **1B** were calculated by the Guassian program[22] using a RHF/6-311G* basis set. The proton–proton scalar coupling constants obtained for the two conformations are listed in Table 2. There are major differences in the coupling constants from the H4a and H4b protons to other protons in the two conformations of the cycloheptane ring moiety. For example, in conformation **1B**, the H4a shows a strong coupling to H6b, and H4b shows a strong coupling to H6a, whereas both of these couplings are absent in conformation **1A**. We focus on the coupling of H4a because it is clearly observed in the experimental NMR spectrum, and there is no overlap with signals from other methylene protons. Although the coupling pattern observed for H4a in the raw experimental NMR spectrum supports a higher population of conformation

Table 2. **Calculated Homonuclear Scalar Coupling Constant Values for Longifolene**

Selected ^{1}H-^{1}H of the cycloheptane ring	Conformation **1A** (J in Hz)	Conformation **1B** (J in Hz)
4a–4b	−15.74	−16.14
4a–5a	0.57	3.73
4a–5b	7.12	3.17
4a–6a	0	1.07
4a–6b	−0.74	6.56
4b–5a	10.97	11.26
4b–5b	0.62	3.43
4b–6a	−0.70	11.42
4b–6b	0	.90
5a–5b	−16.39	−15.41
5a–6a	5.94	0
5a–6b	11.09	−.59
5b–6a	1.29	−.55
5b–6b	6.24	.83
6a–6b	−15.68	−15.76

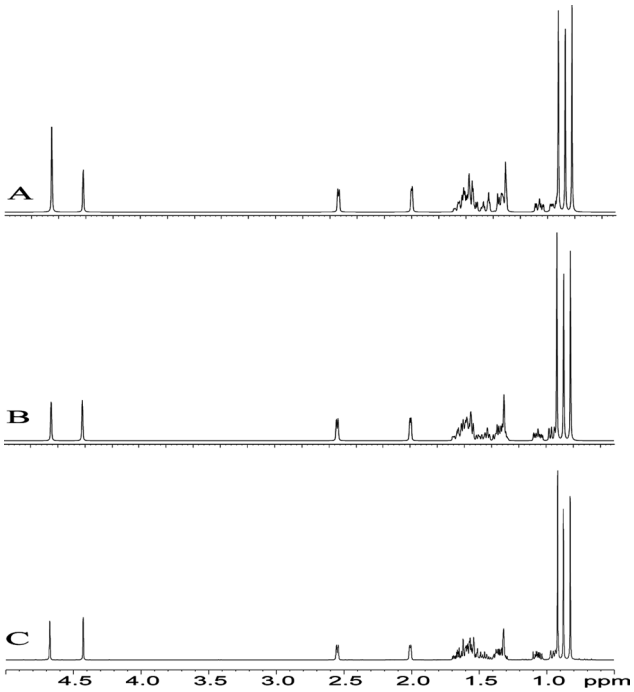

FIGURE 4 **(A) Simulated spectrum from the coupling constants for conformation 1B. (B) Simulated spectrum for conformation 1A. (C) Raw NMR experiment.**

1A, it is essential to compare all of the coupling constants with those of the constants calculated for conformations **1A** and **1B**. Although H2 and H4a protons appear in a "W" conformation in **1A**, no coupling is observed by experiment or predicted by theoretical calculations. Absence of "W" coupling is known for molecules containing bulky substituents capable of interacting with the "W" protons.[25]

In Fig. 4, the experimental raw spectrum of longifolene **C** is compared with the simulated spectra **B** and **A** derived by calculation of conformations **1A** and **1B**. In both simulated spectra, the coupling constants are adjusted in the dense region of 0.80–1.7 ppm. The simulated NMR spectrum **B**, derived for conformation **1A**, closely matches the raw experimental data whereas that of conformation **1B** deviates significantly.

Nuclear Overhauser Analysis

The NOE experiments provide spatial distance data between protons that are separated by less than 5 Å[26] and are very useful in the conformational analysis of longifolene. Strongly coupled protons attached to C4, C5, and C6 in the cycloheptane ring of longifolene along with the lack of dispersion of

chemical shifts make it obscure to study the NOE effects in this region of the molecule. However, methyl protons of C-13b and C-13a, which are not coupled to any other protons, provide useful markers for analyzing NOEs in conformations **1A** and **1B**. The protons on C-13b show a strong NOE to H9 whereas protons on C-13a show a strong NOE to H1. The strength of these NOEs is moderate, which implies an internuclear distance of less than 4 Å and supports conformation **1A**. In conformation **1B**, these NOEs would appear weak or nonobservable as the distances are close to 5 Å.

CONCLUSIONS

Evidence from the NOE and coupling constant measurements shows that the flexible cycloheptane ring moiety in longifolene adopts the twist-chair conformation **1A** in solution. Because of extensive overlap in the cluttered region of 0.80–1.7 ppm, we were unable to accurately measure the coupling constants from NMR experiments. Therefore, we resorted to *ab initio* calculations and simulated the NMR spectra using the gNMR program. Our values of the coupling constants for longifolene are the first reported for the specified region mentioned above. The simulated spectrum of **1A** closely matched the spectrum obtained from the experiment. Variable-temperature NMR experiments reveal a single exchange-averaged NMR spectrum rather than two separate superimposed NMR spectra for each isomer, consistent with a low energy barrier (10 kcal/mole) between **1A** and **1B**. The slight difference in chemical shifts and coupling constants observed in these experiments (Fig. 4) is indicative of minor changes in the mole fraction of the conformers as a result of varying temperatures.

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