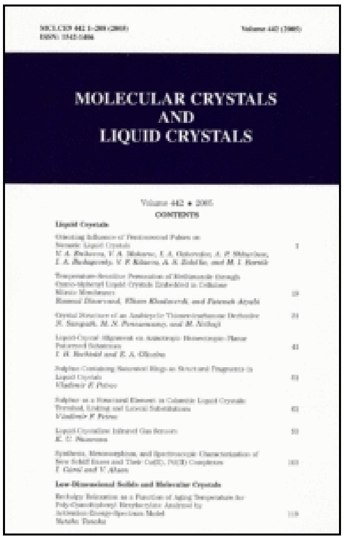

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Determining the Configuration of *Trans*-4-Propyl-Cyclohexylcarboxylic Acid by NMR Method

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Trans-*4-propyl-cyclohexylcarboxylic acid (*Trans-*4-PA) was synthesized. ^1H, ^{13}C, and some 2D nuclear magnetic resonance (NMR) spectra were recorded and signals were assigned. Density functional theory (DFT) calculation was carried out to simulate the optimized* trans- *and* cis-*configuration of 4-PA. Both configurations were stable and in minimal energy states. The dihedral angles of $H_\alpha-C-C-H_\beta$ with respect to carboxylic carbon were measured in both of the two configurations. The Karplus equation was used to speculate on ^3J value of $H_\alpha-H_\beta$ in both configurations. The experimental result was compatible with computed figures of* trans-*configuration. The Fourier transform infrared (FTIR) spectra were also measured and peaks were assigned.*

Keywords Configuration; dihedral angles; Karplus equation; NMR spectroscopy; *trans*-4-propyl-cyclohexylcarboxylic acid

Introduction

Trans-4-alkyl-cyclohexylcarboxylic acid is a class of most widely used liquid crystal materials [1–3]. With 4-alkyl benzoate acid as raw material, a *cis*- and *trans*- mixture (3:1) was obtained through a high-pressure hydrogenation reaction. Then at a higher temperature and higher pressure the isomerization was carried out to transfer the *cis*-form to *trans*-form [4]. Acidic condition [5], basic condition [6], and some special reagents or methylation [7] methods could be used for the isomerization reaction. Mass ratio of *trans*- versus *cis*-form in the final product could be as high as 96:4 (by gas chromatographic [GC] analysis), and a pure *trans*-form could be obtained by simple recrystallization process [8]. Physical properties of *trans*-form were

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different from *cis*-form, usually having a higher melting point. In literature reports, the purity of products was measured by GC [9].

In this article ^1H, ^{13}C, and some 2D nuclear magnetic resonance (NMR) spectra of *trans*-4-propyl-cyclohexylcarboxylic acid (*Trans*-4-PA) were recorded. ^1H and ^{13}C NMR signals were assigned. The Fourier transform infrared (FTIR) spectra were also recorded and main absorbed peaks were assigned. But these data could not prove the absolute configuration of *trans*-4-PA.

There were several ways to determine the absolute configurations of organic compounds through NMR spectroscopy methods, such as non-observed economy (NOE) measurement, method of dihedral angles deduced from ^3J values, and, more recently, measurement of residual dipolar couplings (RDCs) [10]. The dihedral angles is simple and credible determined by the ^3J values. Density functional theory (DFT) calculations provide an optimized molecule structure with minimal energy states. Comparing the experimental result with the molecular structure of calculated results, the absolute configuration of *trans*-4-PA was determined.

Experimental

All chemical reagents used were analytical grade. DMSO-D6 was purchased from Norell Chemical Co., Inc., Landisville, NJ (99.9 atom %D, batch 3024).

Preparation of the Trans-4-Propyl-Cyclohexylcarboxylic Acid

The titled compound was synthesized according to the reported method (Fig. 1) [9]. All chemical reagents used were analytical grade.

A mixture of *cis*- and *trans*-4-PA (n_{cis}:n_{trans} = 25:75) was prepared by hydrogenation reaction in water solvent under 175°C, 9 MPa in the presence of Ni5249P as catalyst [11,12]. Then isomerization was carried out at 195°C and 11 MPa, and the mass ratio of *cis*- and *trans*- was 2:98 [13] when the hydrogenation reaction was stopped. After acidifying and recrystallization, *trans*-4-PA was obtained as white needle crystal, yield 95%, m.p. 98–100°C.

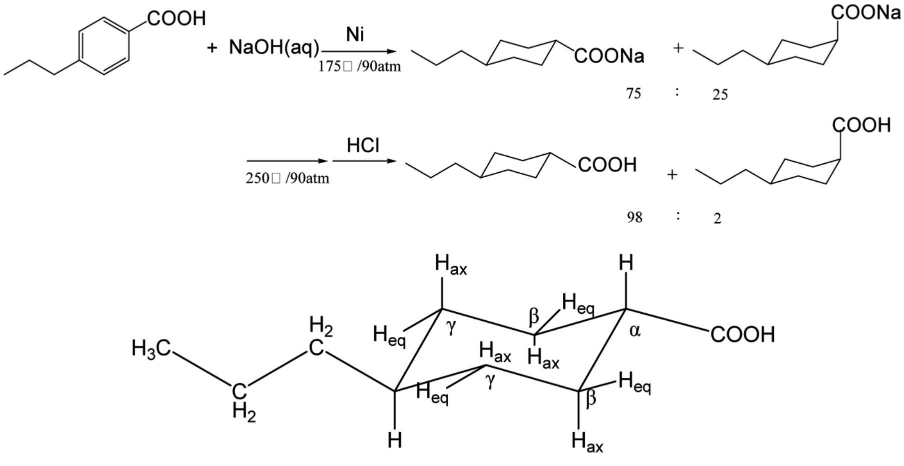

Figure 1. Synthesis process and molecular conformation of *t*-4-PA.

FTIR and NMR Measurement

The IR spectrum was recorded with a Nicolet 6700 FTIR spectrometer, Thermo Fisher Scientific, Waltham, MA, USA. The sample was prepared in KBr matrix with hydraulic press under 14 MPa pressure. The resolution of the spectrometer was set at 4 cm^{-1}.

NMR experiments were performed in a Bruker AVANCE 500 II, Varian, USA, spectrometer using a 5 mm Dual(CH) probe at 300 K. Approximately 5 mg sample was dissolved in 0.5 mL DMSO-D6 for ^1H NMR spectra. ^{13}C NMR and some 2D NMR specta were recorded after adding an additional 20 mg sample to the NMR tube. Chemical shifts were reported in ppm, TMS as reference. ^1H NMR, ^{13}C NMR, two-dimensional correlation spectroscopy (COSY), and Heteronuclear Multiple Quantum Coherence (HMQC) spectra were recorded at a base frequency of 125.76 MHz for ^{13}C and 500.13 MHz for ^1H nuclei. Dept 135, COSY, and HMQC experiments were carried out using standard pulse programs provided in a Bruker Topspin 2.0.

DFT Calculation

Trans- and *cis*- conformations of 4-PA were first built with GaussView, and clean and rebonded tools were used to check the structure. The structure was converted to Gaussian input files. Gaussian was run to carry out DFT calculation by method B3LYP with 6–21 G basis set. Geometrical structures were optimized and frequencies were calculated. In the calculations all frequencies were positive. Therefore, we were confident that a definite absolute minimum in the potential energy surface was found. All the calculations were performed on a personal computer [14].

Results and Discussion

FTIR Spectrum Assignment of t-4-PA

The FTIR spectrum of the titled compound was recorded (Fig. 2), and vibrational peaks were assigned (Table 1).

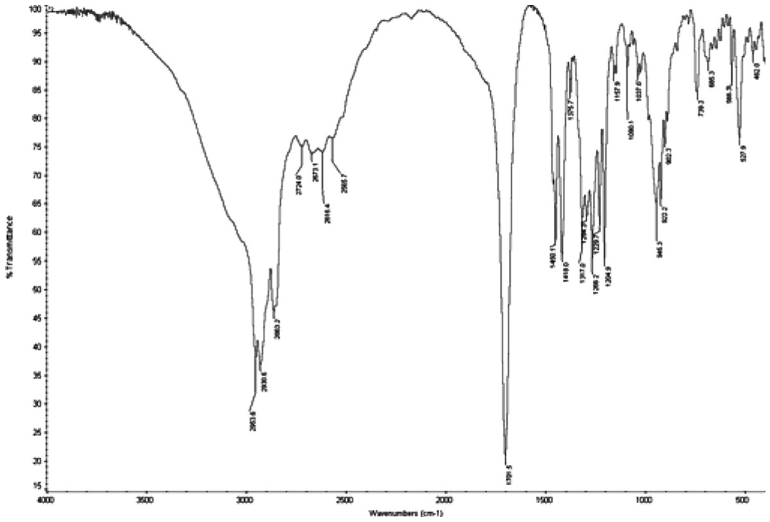

Figure 2. IR spectrum of *trans*-4-PA.

Table 1. Measured IR frequencies (cm^{-1}) of *t*-4-PA molecule and assignment

No.	Frequencies (cm^{-1})	Assignment
1	3300–2500	COO−H, st
2	2953.6	C−H, st
3	2930.6	C−H, st
4	2863.2	C−H, st
5	1701.5	C=O, st
6	1450.1	H−C−H, δ
7	1418.0	H−C−H, δ
8	945.3	C−H, δ

NMR Analysis of trans-4-PA

^1H spectrum showed eight groups of proton signals (see Fig. 3). Total integration values were 18 hydrogen atoms, which agree with the structure of *t*-4-PA. δ_H 11.933 (1H) was a single peak, assigned to a carboxylic acid proton. In the upfield area, δ_H 0.849 (3H) was a triple peak, assigned to methyl. δ_H 2.093 (1H) was a multiple peak and assigned to the H_α proton. δ_H 1.140 (1H) was a multiple peak and assigned to the −CH proton at the 4-position of the ring. The other four groups of signals need more information for assignment.

The *t*-4-PA was in a chair conformation, and the four methylenes in the ring had a planar symmetry. Due to molecular symmetry, eight carbon peaks were observed in ^{13}C spectrum (see Fig. 4). The δ_C values of 2,6-position and 3,5-position carbons were equal. δ_C 177.24 was assigned to the carboxyl carbon. The remaining seven signals were all in the upfield and belonged to alkyl carbons. In DEPT135 spectra δ_C 43.17, δ_C 36.65, and δ_C 14.67 were up peaks. Other signals were down peaks and belonged to $-CH_2$ carbons. In HMQC spectra (Fig. 5), δ_C 43.17 correlated with

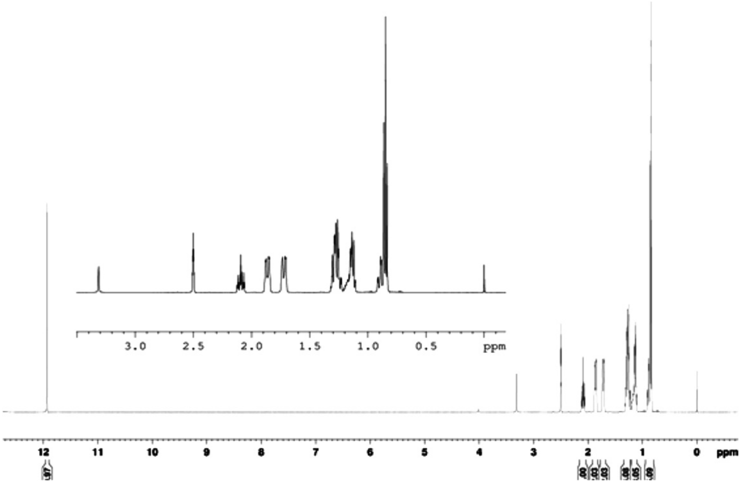

Figure 3. ^1H NMR spectrum of *trans*-4-PA.

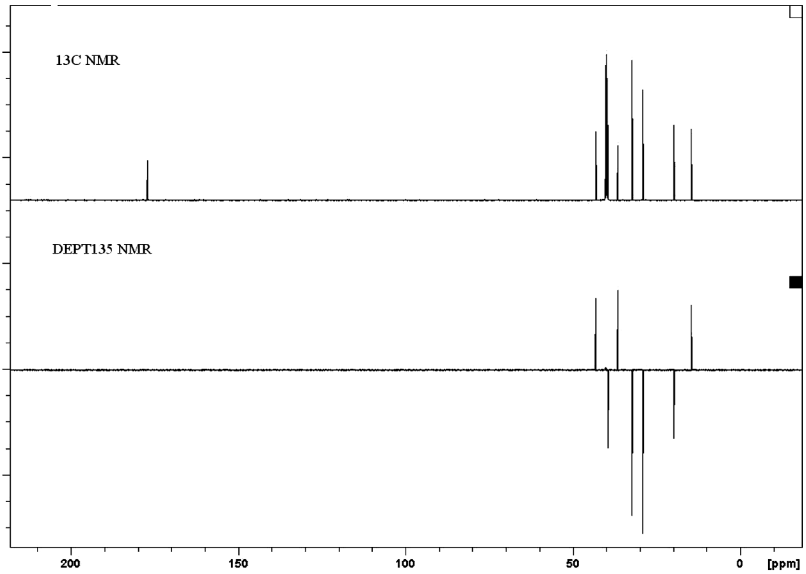

Figure 4. ^{13}C NMR and DEPT 135 spectra of *trans*-4-PA.

δ_H 2.093, assigned to C_α. δ_C 36.65 correlated with δ_H 1.140, assigned to the $-CH$ carbon of the 4-position in the ring. δ_C 14.67 correlated with δ_H 0.849, assigned to the $-CH_3$ carbon.

In the COSY spectrum (Fig. 6), δ_H 2.093 (αH) correlated with δ_H 1.877 (dd, 2H) and δ_H 1.277 (m, two of 4H), so the latter was assigned to four H_β protons. Among

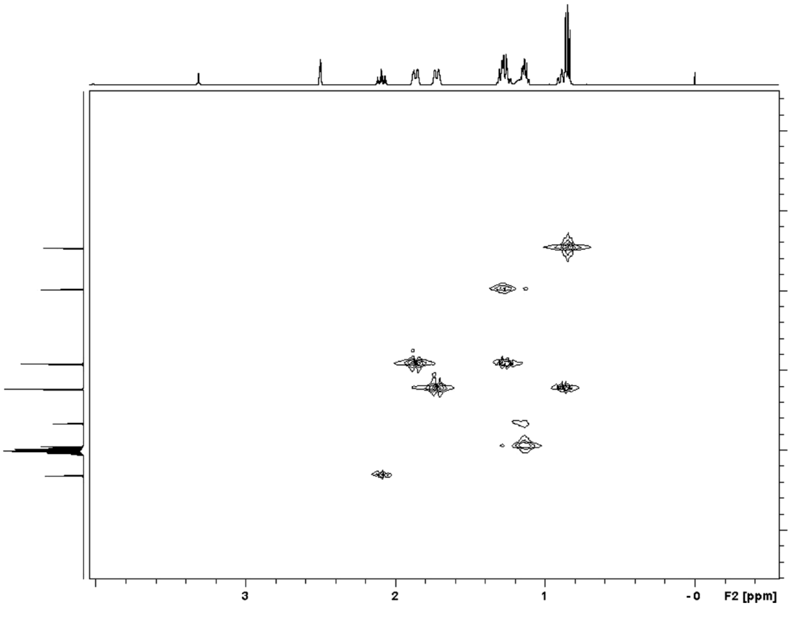

Figure 5. HMQC spectrum of *trans*-4-PA.

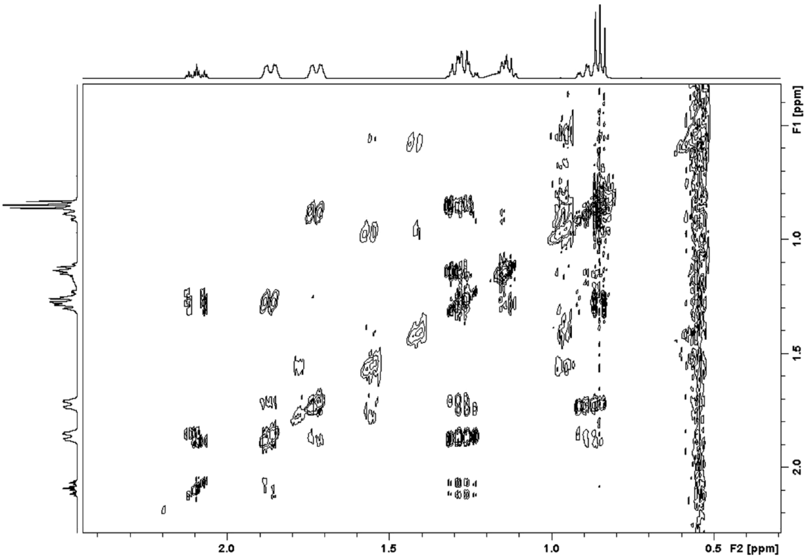

Figure 6. COSY spectrum of *trans*-4-PA.

these, δ_H 1.877 should belong to H_{eq} due to the deshielding effect of the ring. δ_H 1.877 and δ_H 1.277 correlated with δ_H 1.713 (dd, 2H) and δ_H 0.884 (m, 2H), and the latter were assigned to be γH_{eq} and γH_{ax}.

δ_H 1.277 (m, two of 4H) correlated with δ_H 0.849 (signal of $-C\underline{\mathbf{H_3}}$) and was assigned to $-C\underline{\mathbf{H_2}}CH_3$. δ_H 1.130 (m, 2H) correlated with δ_H 1.277 (m, two of 4H, $-C\underline{\mathbf{H_2}}CH_3$) and was assigned to $-C\underline{\mathbf{H_2}}CH_2CH_3$.

In the HMQC spectrum (Fig. 5), δ_C 29.17 correlated with δ_H 1.877 and δ_H 1.277, and was assigned to two C_β atoms in the ring. δ_C 32.30 correlated with δ_H 1.713 (dd, 2H) and δ_H 0.884 (m, 2H) was assigned to $C\gamma$ atoms in the ring. The peak of δ_C 19.84 and δ_C 39.51 were assigned to be signals of $-\underline{C}H_2CH_3$ and $-\underline{C}H_2CH_2CH_3$. The total assignments of ^1H and ^{13}C NMR spectra are summed up in Table 2.

Table 2. Assignment of NMR data of *trans*-4-PA

No.	δ_C	δ_H	Assignment
1	14.67	0.849 (t, 3H)	$-CH_3$
2	19.84	1.277 (m, two of 4H)	$-\underline{\mathbf{CH_2}}CH_3$
3	29.17	1.877 (dd, 2H)	βCH_{eq}
4	29.17	1.277 (m, two of 4H)	βCH_{ax}
5	32.30	1.713 (dd, 2H)	γCH_{eq}
6	32.30	0.884 (m, 2H)	γCH_{ax}
7	36.65	1.140 (m, 1H)	4-position CH in ring
8	39.51	1.130 (m, 2H)	$-\underline{\mathbf{CH_2}}CH_2CH_3$
9	43.17	2.093 (tt, 1H)	αCH
10	177.24	11.933 (s, 1H)	$-COOH$

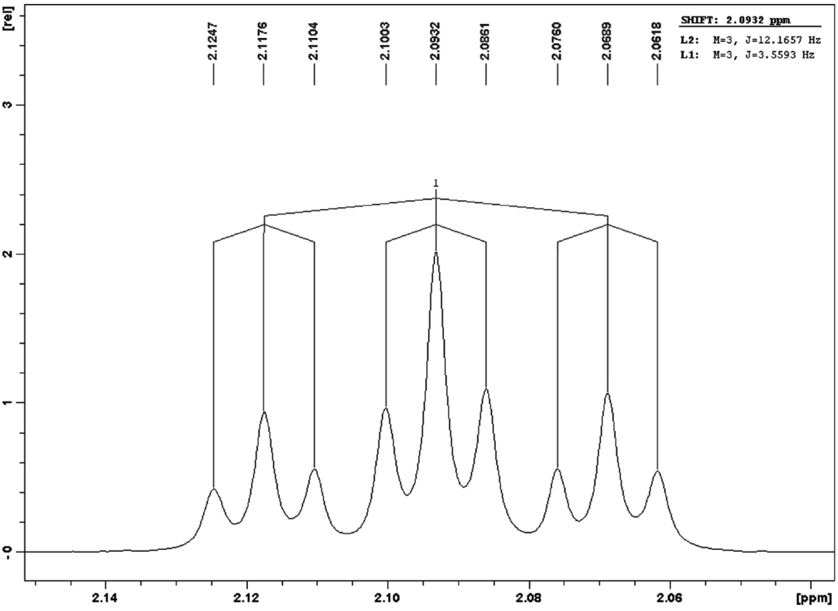

Figure 7. Multiplet analysis of α-H signal.

Automatic multiplet analysis program in Bruker Topspin 2.0 software was used to deduce coupling constants of the multiple peak of δ_H 2.093. Two ^{3}J values were acquired as 12.2 and 3.6 Hz (Fig. 7).

Molecular Conformational Study

DFT calculation showed that the *trans*- and *cis*-configurations of 4-PA were both in minimal energy states. The E value of the *trans*-configuration was −539.4325 A.U, lower than *cis*- of −539.4292 A.U. So the latter could be converted to *trans*- under thermodynamic rule.

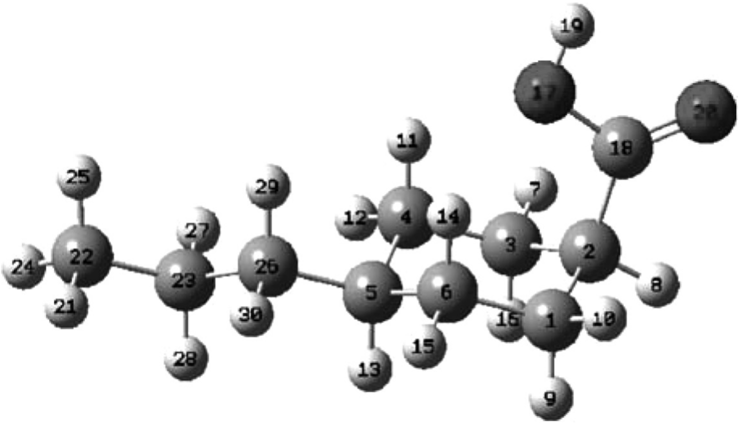

Figure 8. Optimized configuration of *cis*-4-PA.

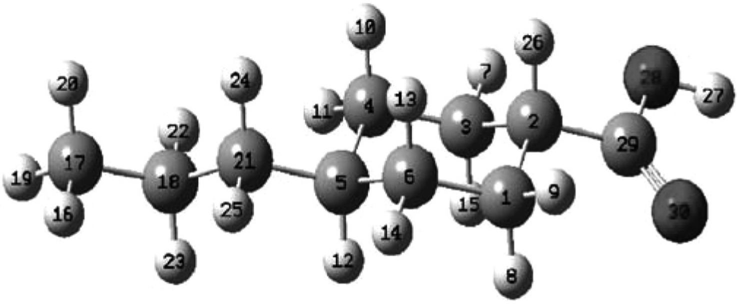

Figure 9. Optimized configuration of *trans*-4-PA.

The optimized configurations of *trans*- and *cis*-4-PA are shown in Figs. 8 and 9. In both configurations the four dihedral angles (H_α and H_β) were measured (Table 3).

The Karplus equation is a semi-empirical calculation method for the relationship between ^3J and dihedral angles.

$$^3J = J^0 \cos^2 \Phi - 0.3 \quad 0^\circ \le \Phi \le 90^\circ$$

$$^3J = J^{180} \cos^2 \Phi - 0.3 \quad 90^\circ \le \Phi \le 180^\circ$$

If J^0 and J^{180} were difficult to obtain, the semi-empirical curve could be used to speculate on approximate ^3J values (Fig. 10).

Because we had the optimized conformations of *trans*- and *cis*-configurations of 4-PA, it was easy to speculate on ^3J values (coupling constant between H_α and H_β). In the case of the *cis*-configuration, there were two angles of 49.3 degrees and two angles of 66.7 degrees. There should be two ^3J values; one was 4.0 Hz and another was approximately 2.0 Hz. In the case of *trans*-configuration, there were two angles of 176 degrees (175.8 degrees and 176.3 degrees)and two angles of 59 degrees (58.3 degrees and 59.7 degrees). There should be two ^3J values; one was 14.5 Hz and another was approximately 3.0 Hz. The measured ^3J values were 12.2 and 3.6 Hz, so the product must be *trans*-configuration.

Table 3. Dihedral angles between H_α and H_β in both *cis*- and *trans*-configurations

	Dihedral angle	Measurement data
Cis-configuration	H8–C2–C3–H7	66.7
	H8–C2–C3–H16	49.3
	H8–C2–C1–H10	66.7
	H8–C2–C1–H9	49.3
Trans-configuration	H26–C2–C3–H7	58.3
	H26–C2-C3–H15	175.8
	H26–C2–C1–H9	59.7
	H26–C2–C1–H8	176.3

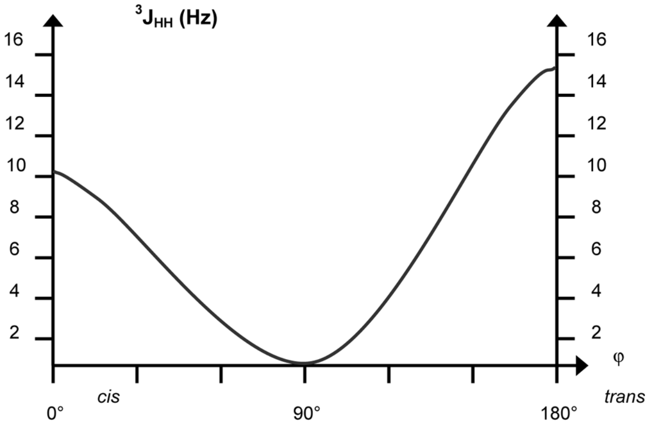

Figure 10. $^3J_{\text{H-H}}$: Information about torsion angle.

Conclusion

4-Propyl-cyclohexylcarboxylic acid (mixture of *cis*- and *trans*-configuration) was synthesized through the hydrogenation reduction of 4-propyl-benzoate acid. After the isomerization reaction, a pure *trans*-configuration product was obtained. ^{1}H, ^{13}C, and some 2D NMR spectra of *t*-4-PA were measured and signals assigned.

DFT calculation was carried out to simulate the optimized *trans*- and *cis*-configurations of 4-PA. Both configurations were stable and in minimal energy states. The four dihedral angles of H_α–C–C–H_β of carboxylic carbon were measured in both of the two configurations. The Karplus equation was applied to speculate on ^{3}J values (H_α–H_β) of both *trans*- and *cis*-configurations. The experimental data were compatible with the computed result of *trans*-configurations. The FTIR spectra were also recorded and main absorbed peaks were assigned.

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