

**Nuclear Magnetic Resonance Spectroscopy.
Variable-Temperature ^{13}C and ^{19}F Study of
the Chair-Chair Interconversion of
1,1,3,3-Tetramethylcyclohexane and
gem-Difluoro-1,1,3,3-Tetramethylcyclohexanes***

**David Doddrell, Claude Charrier, Bruce L. Hawkins, W. O. Crain, Jr.,
Leland Harris, and John D. Roberts**

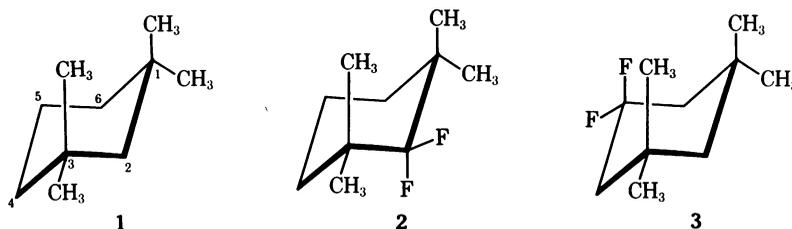
GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY,
PASADENA, CALIF. 91109

Communicated September 3, 1970

Abstract. A variable-temperature, proton noise-decoupled, ^{13}C nmr spectral study of the chair-chair interconversion in 1,1,3,3-tetramethylcyclohexane has demonstrated the utility of ^{13}C spectra for probing conformational equilibria. There is a much larger chemical-shift difference between the carbons of axial and equatorial methyl groups than between the protons of these methyl groups, 133 Hz compared to 7.5 Hz. Comparison of the activation parameters determined from the ^{13}C spectra of 1,1,3,3-tetramethylcyclohexane with those determined from a variable-temperature ^{19}F study on 2,2,6,6-tetramethyl-1,1-difluorocyclohexane shows that the introduction of a *gem*-difluoro group into the ring causes significant steric interactions. The ^{13}C chemical shifts for 1,1,3,3-tetramethylcyclohexane reflect the importance of the methyl-methyl 1,3-diaxial interactions.

The utility of variable-temperature, high-resolution, ^1H and ^{19}F magnetic resonance for the investigation of conformational equilibria, and rates of ring inversion, in cyclohexane and substituted cyclohexanes is well known.¹ However, investigations with the cyclohexane nucleus are often complicated by small chemical-shift differences between axial and equatorial sites and hence, low coalescence temperatures for the resonances as well as complex splitting patterns, which make total line-shape analysis difficult or impossible. Although the "fluorine-labeling" technique alleviates some of these difficulties, problems can arise in relating the resultant equilibrium constants and activation parameters to those of the hydrogen analogs.¹ Variable-temperature ^{13}C nmr spectra with proton noise decoupling are expected to solve some of these problems because of the inherently larger chemical shifts and simplified spectra compared to those of hydrogen. We describe here comparisons of the rates and activation parameters derived from the ^{13}C spectra of 1,1,3,3-tetramethylcyclohexane (**1**), and those from a ^{19}F study on the related difluorides, **2** and **3**.

The ^{13}C spectrum of **1** was investigated over the temperature range -107 to -39°C . The coalescence temperature for the methyl carbons is about -80°C



and the peaks are separated by 133 Hz at the low-temperature limit. At -107°C the chair-chair interconversion is not completely halted on the nmr time-scale, but the two methyl singlets are almost sharpened to full height. The spectra were fitted using an iterative procedure, and the experimental and calculated spectra are shown in Fig. 1. The invariant peak is the quaternary carbon resonance, the line width of which was used to estimate T_2^* . An Arrhenius plot of the data (Fig. 2) gave the activation parameters listed in Table 1.

At $+39^{\circ}\text{C}$, the ^{19}F spectrum of **2** appeared as a broad singlet, 6608 Hz upfield from fluorotrichloromethane. At lower temperatures, the resonance broadened further and reached its maximum width at the coalescence temperature of approximately -38°C . At -93°C , the typical AB pattern was observed, with ν_{eq} and ν_{ax} equal to $+6176$ and $+7022$ Hz, respectively, with $J_{\text{F-F}}$ as 246 Hz. Similar behavior was noted for **3**, wherein a quintet at $+39^{\circ}\text{C}$ ($+4855$ Hz and $J_{\text{H-F}} = 15$ Hz) broadened until the coalescence temperature of approximately -100°C was reached, then sharpened to an AB pattern at -146°C ($\nu_{\text{eq}} = +4282$ Hz, $\nu_{\text{ax}} = +4958$ Hz, $J_{\text{F-F}} = 244$ Hz). Total line-shape analysis of the spectra of **2** and **3**, combined with a least-squares Arrhenius plot of the data, gave the parameters listed in Table 1.²

It is interesting that the experimental E_a for **1**, 6.8 kcal/mole, is 4.2 kcal/mole smaller than that for cyclohexane itself³; this difference is very close to the difference of 4.7 kcal/mole calculated by Allinger⁴ for the difference in ground-state strain energies between cyclohexane and **1**, ascribable to 1,3-dimethyl axial interactions. From this, we can conclude that the strain in the transition state for cyclohexane and **1** is likely to be nearly equal.

Comparison of the E_a and ΔG^\ddagger values between the cyclohexanes shows that the introduction of two fluorine atoms onto the ring alters the energetics of the inversion process. Cyclohexane **2** has larger E_a and ΔG^\ddagger values than **1**, consistent with destabilization of the transition state for the inversion as a result of 1,2 fluorine-methyl interactions. However, **3** has smaller E_a and ΔG^\ddagger values than **1**, which can be ascribed to destabilization of the ground state of **3** relative to **1** arising from 1,3 diaxial fluorine-methyl interactions. Hence, it is apparent that the "fluorine-labeling" technique here leads to somewhat different activation parameters than for the hydrogen analogs, either by destabilization of the ground, or of the transition states, for the inversion process. The value of ΔG^\ddagger for **1** obtained in this study is in reasonable agreement with the value of 9.6 kcal/mole recently determined by a ^1H study,⁵ considering that the methyl-proton chemical-shift difference was only 7.5 Hz (at 100 MHz) at -91°C , compared with a ^{13}C methyl chemical-shift difference of 133 Hz (at 15.1 MHz) in the low-temperature

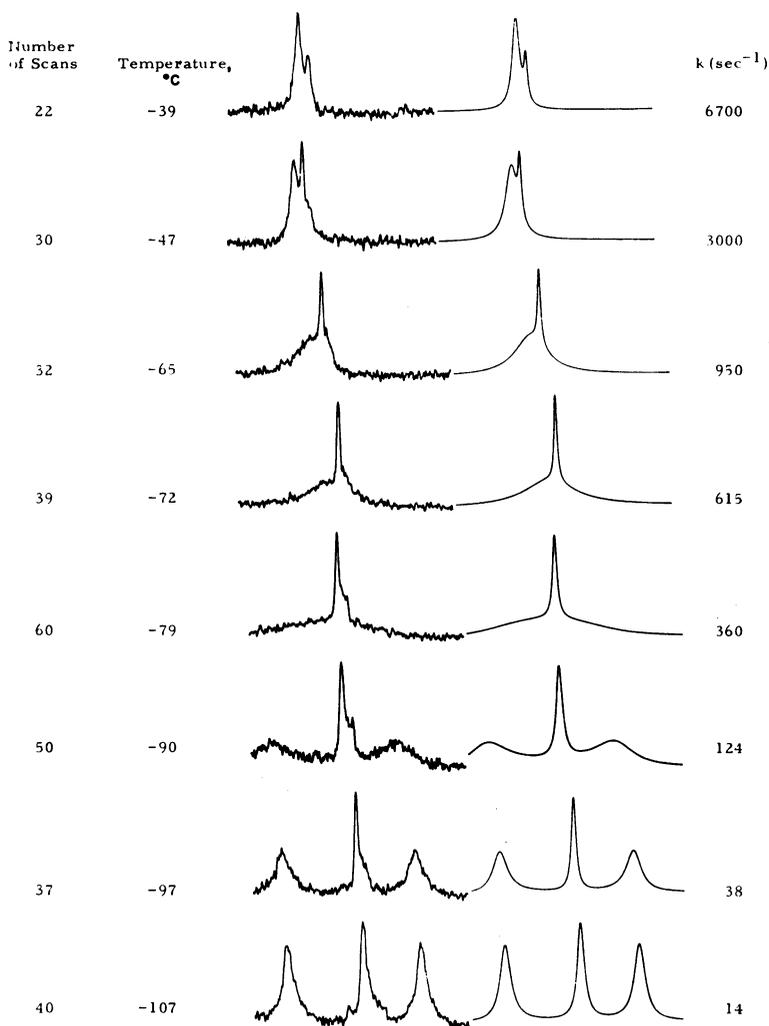
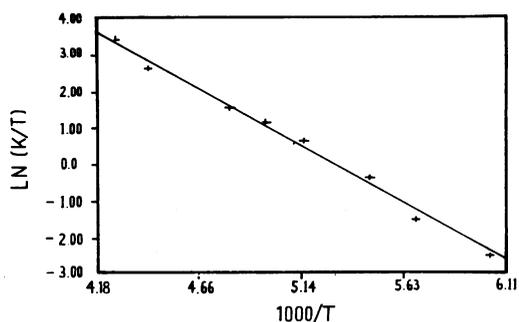


FIG. 1. Calculated (*right*) and experimental (*left*) ^{13}C spectra for the methyl region of **1**.

limit. This contrast, although expected, serves to illustrate the potential of variable-temperature ^{13}C magnetic resonance in conformational analysis.

It is instructive to compare the ^{13}C chemical shifts obtained for **1** to other methyl-substituted cyclohexanes. The shifts for *trans*-1,3-dimethylcyclohexane (**5**, Table 2) were recorded for a neat sample at -87°C . The shifts for methylcyclohexane (**4**), and 1,1,3-trimethylcyclohexane (**6**), listed in Table 2, are those reported by Dalling and Grant.⁶ It is apparent that the observed ^{13}C shifts of **1** are significantly affected by methyl-methyl 1,3-diaxial interactions. Introduction of an axial methyl group does not usually affect the ^{13}C chemical shift of an equatorial methyl group three bonds away—note the minor change in the $\text{CH}_3(e)$ chemical shift between **4** and **5**, and the small chemical-shift change between

FIG 2. Arrhenius plot for the chair-chair interconversion of 1.



$\text{CH}_3(e)$ in **4** and $\text{CH}_3(3)$ in **6**. However, for **1**, the 1,3-diaxial methyl interactions appear to cause a significant downfield shift (3.4 ppm) of the equatorial methyl three bonds away—compare the $\text{CH}_3(e)$ shifts between **1** and **6**.

The γ_a methyl substituent effect⁶ is normally on the order of ± 5 ppm (compare the C-1 carbons and the C-5 carbons of **4** and **5**). It might be expected that

TABLE 1. Activation parameters for the cyclohexanes **1**, **2**, and **3**.

| Compound | $\ln A$ | ΔE_a (kcal/ mole) | ΔG^\ddagger (kcal/ mole) | ΔH^\ddagger (kcal/ mole) | ΔS^\ddagger (eu.) |
|--|---------------------|---------------------------------|--|--|------------------------------|
| 1,1,3,3-Tetramethyl- cyclohexane (1) | 23.4 $\pm 0.5^*$ | 6.8 ± 0.2 | 9.0 ± 0.1 | 6.4 ± 0.2 | -13.2 ± 1.0 |
| 2,2,6,6-Tetramethyl-1,1- difluorocyclohexane (2) | 29.7 ± 0.3 | 10.3 ± 0.1 | 10.1 ± 0.1 | 9.8 ± 0.1 | -1.0 ± 0.5 |
| 3,3,5,5-Tetramethyl-1,1- difluorocyclohexane (3) | 25.1 ± 0.5 | 6.2 ± 0.2 | 7.4 ± 0.1 | 5.8 ± 0.2 | -9.0 ± 1.0 |

* The errors are 50% confidence intervals obtained from a statistical treatment of the data and ignoring systematic errors [see Wentworth, W. E., *J. Chem. Ed.*, **42**, 96, 162 (1965)]. Of the activation parameters, those listed for ΔG^\ddagger are considered to be the most accurate. The values given are the averages over the temperature range studied.

TABLE 2. ^{13}C chemical shifts of methylcyclohexane derivatives.

| Carbon | 1 | 4 | 5 | 6 |
|------------------|--------|-------|-------|-------|
| 1 | 161.3* | 160.4 | 165.0 | 162.7 |
| 2 | 139.6 | 157.7 | 152.1 | 144.2 |
| 3 | 161.3 | 166.9 | 166.6 | 165.2 |
| 4 | 152.5 | 167.1 | 161.6 | 157.8 |
| 5 | 172.2 | 166.9 | 172.2 | 170.9 |
| 6 | 152.5 | 157.7 | 157.1 | 154.0 |
| $\text{CH}_3(e)$ | 156.4 | 170.7 | 169.8 | 159.8 |
| $\text{CH}_3(a)$ | 165.2 | — | 174.8 | 168.6 |
| $\text{CH}_3(3)$ | — | — | — | 170.4 |

* Chemical shifts are in ppm upfield from carbon disulfide, and for compounds **1** and **5** at -107 and -87°C , respectively.

the 1,3-diaxial interaction between the methyls in **1** would result in a sizable upfield shift of the resonance of C-1, relative to the resonance of C-1 of **6**. However, only a small downfield shift is observed which, in fact, accords with Grant's theory⁶ that steric hindrance exerting force perpendicular to, rather than along, the bonds will not produce large chemical-shift changes. The very large sequence of downfield shifts at C-2 in the progression from **4** → **5** → **6** → **1** is understandable in terms of interactions elongating the C-C bonds of C-2.⁷

* Supported by the National Science Foundation. Contribution no. 4083 from the Gates and Crellin Laboratories.

¹ Spassov, S. L., D. L. Griffith, E. S. Glazer, K. Nagarajan, and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 88 (1967) and references cited therein. Stolow, R. D., T. W. Giants, and J. D. Roberts, *Tetrahedron Lett.*, **55**, 5777 (1968); Roberts, J. D., *Chem. Brit.*, **2**, 529 (1966).

² Variable-temperature ¹³C spectra were taken of a 40% solution of **1** in CS₂, contained in a 10-mm spinning tube, with the aid of the DFS-60 spectrometer described by Weigert, F. J., and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 2967 (1967). The ¹⁹F spectra of **2** and **3** were recorded at 56.4 MHz with a Varian Model A-56/60 spectrometer, using dimethyl ether as solvent. The temperatures were measured with a copper-constantan thermocouple having the reference junction at 0°C, and a Leeds and Northrup Co. potentiometer. The difluorides were prepared from the corresponding cyclohexanones (Aldrich) with sulfur tetrafluoride as described by Hasek, W. R., W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960).

³ Anet, F. A. L., and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **89**, 760 (1967).

⁴ Allinger, N. L., J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *J. Amer. Chem. Soc.*, **90**, 1199 (1968).

⁵ Friebolin, H., H. G. Schmid, S. Kabuss, and W. Faisst, *Org. Mag. Res.*, **1**, 147 (1969).

⁶ Dalling, D. K., and D. M. Grant, *J. Amer. Chem. Soc.*, **89**, 6612 (1967). Professor Grant (private communication) has also examined the temperature dependence of the ¹³C spectrum of *trans*-1,3-dimethylcyclohexane and other inverting dimethylcyclohexanes.

⁷ Roberts, J. D., F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, **92**, 1338 (1970); Grutzner, J. B., M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Amer. Chem. Soc.*, in press.