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# RING INVERSION IN 1,1,4,4-TETRAMETHYLCYCLOHEXANE

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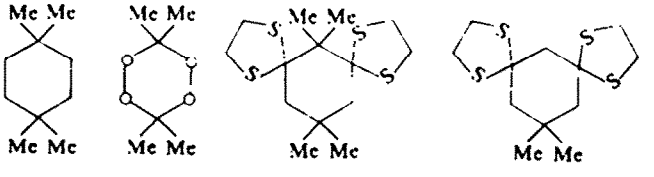
**Abstract**—The rate of conformational isomerization of 1,1,4,4-tetramethylcyclohexane has been measured over the temperature range −75° to −40° by observing the NMR spectrum. Using an equation for rapid exchange as well as an IBM 7090 computer program the parameters Ea, $\nu_0$, $\Delta F^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ have been obtained. The coalescence temperature for the 5,5-dimethyl group has been measured in the bis-dithioketals of 2,2,5,5-tetramethylcyclohexane-1,3-dione and 5,5-dimethylcyclohexane-1,3-dione and used to calculate $\Delta F^{\ddagger}$ for the isomerization process.

THE study of conformational isomerization in cyclohexane derivatives and other systems has received increasing attention over the past 5 years largely because of the information available from variable temperature NMR studies.[1] This technique has permitted the evaluation of the transition state parameters for the isomerization process in cyclohexane, some substituted cyclohexanes, and other cyclic compounds.

When this work was begun there was only one report of the determination of the barrier to conformation isomerization in an alkyl cyclohexane.[2] Presumably this was due to the fact that the barriers may be very low and hence inaccessible with the usual equipment or to the difficulties encountered when one has unequal populations of the chair forms.

Recently, however, two reports have appeared on the temperature dependence of the NMR spectrum of 1,1,4,4-tetramethylcyclohexane (I). Reusch and Anderson[3] have shown that the spectra obtained establish the chair conformation in I and give the coalescence temperature for the methyl resonance as −65° (60 MC). These authors




I II IV V

report the chemical shift difference between the axial and equatorial Me groups to be 0·04 ppm at −78°. Friebolin *et al.*[4] have also measured the low temperature NMR spectrum of I. Using a 100 MC spectrometer these workers report a coalescence temperature of −53° and a chemical shift difference of 6 c/s for the axial and

[1] For a description of the applications of this technique see J. E. Anderson, *Quart. Revs.* **19**, 426 (1966) and L. W. Reeves in *Adv. Phys. Org. Chem.* **3**, 187 (1965).
[2] I. Yamaguchi and S. Brownstein, *J. Phys. Chem.* **68**, 1572 (1964).
[3] W. Reusch and D. F. Anderson, *Tetrahedron* **22**, 583 (1966).
[4] H. Friebolin, W. Faisst, H. G. Schmid and S. Kabuss, *Tetrahedron Letters* 1317 (1966).

equatorial Me groups. They have also calculated $\Delta F^{\ddagger}$ for the barrier to conformational isomerization to be 11·6 kcal/mole.

While it is possible to obtain a value for $\Delta F^{\ddagger}$ from the coalescence temperature alone, measurements over a range of temperatures are necessary in order to obtain values for the other parameters, a process which is often beset with experimental difficulties,[5] particularly when $\Delta\nu$, the chemical shift difference between the axial and equatorial groups, is small compared to the linewidth, as is true in the present case. By making measurements over a temperature range and using a computer program to obtain comparison curves, rate constants could be determined at a number of temperatures, and the desired thermodynamic quantities calculated. The usable temperature range is still limited to that in which exchange contributions to relaxation are dominant.[5] In the present case this range is 35°. At temperatures above −40° and below ca. −75° non-exchange line effects are dominant.

The barrier to isomerization in I was of particular interest to us in order to compare it to that recently reported[6] for acetone diperoxide (II), the analog of I in which four of the ring carbon atoms have been replaced by oxygen. In the present work the NMR spectrum of I was measured in the range −40 to −75° and the results used to calculate Ea, $\nu_0$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, in addition to $\Delta F^{\ddagger}$, as reported by Friebolin *et al.*[4]

The synthesis of I used varies only slightly from that described.[3] Dimedone III (5,5-dimethyl-1,3-cyclohexanedione) was converted to 2,2,5,5-tetramethylcyclohexane-1,3-dione using sodium methoxide and methyl iodide. The diketone was then converted to the bis-dithioketal (IV) which was reduced to I using Raney nickel W-7 catalyst in refluxing ethanol.

The NMR spectrum of I at 37° consists of two sharp singlets at 8·72 and 9·13[7] with an integrated area ratio of 2:3·2. These absorptions are assigned to the methylene and Me protons, respectively. At −80° the spectrum consists of a broad methylene absorption at 8·78 while the Me absorption is now split into two sharp singlets at 9·16 and 9·11. As reported,[3] these observations confirm that I exists in rapidly interconverting chair conformations which are "frozen out" at the low temperature, thus permitting observation of the separate axial and equatorial methyl absorptions. Following the usual rule for assignment in cyclohexane systems[8] the lower chemical shift absorption is assigned to the equatorial Me groups.

The spectrum of I in the temperature range −39° to −58° was measured on a Varian A-60 Spectrometer while that in the range −58° to −75° was measured on a Varian DA-60-EL Spectrometer.[9] The observed linewidth reflects contributions from field inhomogeneity and instability and a contribution from $T_2^0$, the transverse relaxation time in the absence of exchange, in addition to the exchange broadening of interest in the present work. The observed linewidth was corrected for non-exchange contributions by subtracting the width of the tetramethylsilane (TMS) reference line at each temperature. The resulting linewidths in the range above

[4] A. Allerhand, F. -M. Chen and H. S. Gutowsky, *J. Chem. Phys.* **42**, 3040 (1965).
[5] R. W. Murray, P. R. Story and M. L. Kaplan, *J. Amer. Chem. Soc.* **88**, 526 (1966).
[7] Chemical shift values given are tau values relative to internal TMS in $CS_2$ soln.
[8] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* Section 7.2. Pergamon Press, New York (1959).
[9] We wish to acknowledge the valuable assistance of Mr. E. W. Anderson in determining the NMR spectra in this range.

coalescence can be used to calculate $\tau$, the residence time, from Eq. (1).[10]

$$\frac{1}{T_2'} = \frac{P_A}{T_{2A}} + \frac{P_B}{T_{2B}} + P_A^2 P_B^2(\omega_A - \omega_B)^2(\tau_A + \tau_B) \quad (1)$$

In the present case there are equal populations and lifetimes of the two positions so that,

$$P_A = P_B = \tfrac{1}{2} \qquad \text{and} \qquad \tau_A = \tau_B = 2\tau$$

the equation for the effective transverse relaxation time, therefore reduces to:

$$\frac{1}{T_2'} = \frac{1}{T_{2\,ref.}} + \tfrac{1}{4} \cdot \delta\omega^2 \cdot \tau$$

Where $1/T_{2\,ref.}$ is obtained from the TMS linewidth, $\delta\omega$ is the separation between the peaks in the absence of exchange, which was found to be 3·85 c/s, and $\tau$ is the residence time as defined by Gutowsky and Holm.[11]

In order to extend the temperature range over which the rate of isomerization was measured a FORTRAN computer program[12] was used to plot the line shape function using an IBM 7090 computer. The computer program is entered with values of $1/T_2$, that is, nonexchange contributions to line broadening and values of $\tau$, the residence time. The values of $1/T_2$ were chosen as variations of those experimentally observed on the TMS reference line. The computer-generated line shapes were then compared to the experimental curves and matched on the basis of linewidth (above coalescence) or peak-to-valley ratio (below coalescence) to give values of $\tau$. Some representative experimental curves are shown in Fig. 1.

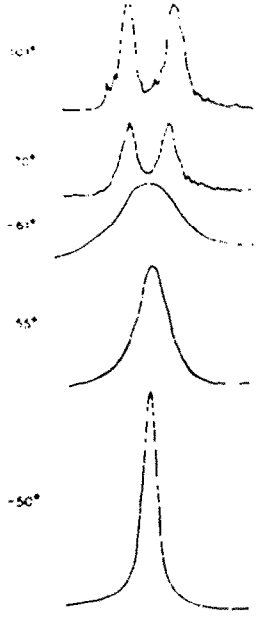



FIG. 1. Representative NMR spectra of I at various temperatures.

[10] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* p. 222. McGraw-Hill, New York (1959).

[11] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.* **25**, 1228 (1956).

[12] We are grateful to Dr. M. Cocivera for providing us with this program and for helpful discussions of this problem.

Arrhenius plots of the rate constants obtained from Eq. (1), and from comparing experimental and computer-drawn curves are shown in Fig. 2. In this treatment the rate constant for the rate of chair-to-chair isomerization $k = 1/2\tau$, since $1/\tau$ represents the sum of the rates of inversion in both directons.[11] The least squares method was used to calculate $E_a$ and $\nu_0$, the frequency factor, from both sets of data. Use of the data from Eq. (1) gives values of $13{\cdot}3 \pm 3{\cdot}2$ kcal/mole and $4{\cdot}19 \times 10^{14}$ sec$^{-1}$ for Ea and $\nu_0$, respectively. The points obtained from computer matching give $13{\cdot}7 \pm 1{\cdot}5$ kcal/mole and $1{\cdot}17 \times 10^{15}$ sec$^{-1}$ for Ea and $\nu_0$, respectively. The maximum error in Ea was determined by calculating the standard error of estimate of the least squares line and then computing max and min slopes. The points obtained from Eq. (1) have a lot of scatter as reflected in the large experimental error quoted for Ea. However, it can be seen that by using computer curve matching the available temperature range was extended and the experimental error in Ea reduced.

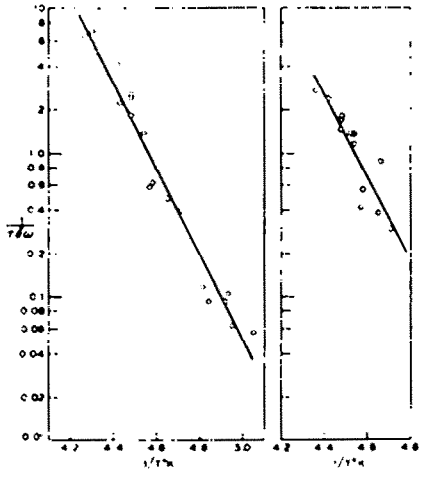


FIG. 2. Temperature dependence of the conformational isomerization rate constant for I. The plot on the right is based on data from Equation I while that on the left is based on computer curve matching data.

The Eyring formulation was then used to calculate the transition state parameters at the coalescence temperature as follows,

$$\Delta F^{\ddagger} = 2{\cdot}3RT(10{\cdot}32 + \log T - \log k)$$

$$\Delta H^{\ddagger} = Ea - RT$$

$$\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta F^{\ddagger})/T$$

A summary of the data obtained as well as that reported[4] is given in Table 1.

The value obtained for $\Delta F^{\ddagger}$ in this study is in good agreement with that reported.[4] These values indicate that the barrier in the tetramethyl-substituted cyclohexane is only slightly higher than the 10·2[13] or 10·3[6] kcal/mole reported for cyclohexane. The values given for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are subject to the relatively large errors quoted for Ea and therefore, $\Delta S^{\ddagger}$, in particular, is perhaps only meaningful to the extent of saying that there is a small positive entropy of activation.

The description given has assumed a transmission coefficient of unity. If it is

[11] F. A. Bovey, F. P. Hood, III, E. W. Anderson and R. L. Kornegay, *J. Chem. Phys.* **41**, 2041 (1964)

TABLE 1. SUMMARY OF ISOMERIZATION RATE PARAMETERS FOR SOME CYCLOHEXANE DERIVATIVES

| Compound | Temp., °K | $\Delta F^{\ddagger}$cc, kcal/mole | $\Delta H^{\ddagger}$, kcal/mole | $\Delta S^{\ddagger}$ e.u. | Ea, kcal/mole | Ref |
|---|---|---|---|---|---|---|
| I | 220 | 11·6 | --- | — | — | 4 |
| I | 211 | 11·4 | 13·3 | 9·1 | 13·7 ± 1·5 | This work |
| II | 303 | 15·4 | 11·7 | −12·1 | 12·3 ± 0·9 | 6 |
| IV | 207 | 10·4 | -- | — | — | This work |
| V | 187 | 9·41 | — | — | — | This work |
| $C_6H_{12}$ | 206 | 10·3* | 9·1 | −5·8* | 9·5 ± 0·5 | 5 |
| $C_6H_{12}$ | 206 | 10·2* | 10·5 | 1·4* | — | 13 |

* These values are for the chair-to-boat process.

assumed that a molecule in the barrier form, which presumably is in some type of boat form, has an equal chance of going forward to the other chair form as going back to the starting chair form, then the rate of chair to boat isomerization, $k_{cb}$, must be twice that of the observed chair-to-chair rate, $k_{cc}$. The $\Delta F^{\ddagger}$ for the chair-to-boat process is then,

$$\Delta F_{cb}^{\ddagger} = \Delta F_{cc}^{\ddagger} - 2{\cdot}3RT \log 2$$

$$\Delta F_{cb}^{\ddagger} = 11{\cdot}1 \text{ kcal/mole}$$

The $\Delta F^{\ddagger}$ for I is approximately 4 kcal/mole lower than that for acetone diperoxide (II).[6] The difference probably reflects the additional energy requirements imposed by the shorter bond lengths, smaller bond angles and perhaps the steric requirements of the oxygen nonbonding electrons in II. The value of $\Delta F^{\ddagger}$ for II, as calculated from coalescence temperature, was found to be within experimental error of the value reported[6] for deuteriochloroform when the isomerization was measured in methanol, tetrachloroethylene, deuterioacetone or a mixture of carbon disulfide and chloroform. It seems unlikely therefore that the observed difference in $\Delta F^{\ddagger}$ between I and II is attributable to a solvent effect.

Reusch and Anderson also reported[3] the interesting observation that only one of the two *gem* dimethyl groups in IV splits into separate peaks when the temperature is lowered. By comparing chemical shift values in the NMR spectrum of IV to those in the bis-dithioketal (V) of dimedone these authors were able to show that the dimethyl group which is not splitting is the one located between the dithioketal groups. They suggested that the bracketing of this dimethyl group by the dithioketal groups serves to eliminate the chemical shift difference between the axial and equatorial Me groups.

We have confirmed these observations and further have measured the coalescence temperatures for the methyl coalescence in IV and V, thus permitting an estimate of the relative energy barriers to conformational isomerization. Measuring the low temperature spectrum of V provides an additional check on the *gem* dimethyl group assignments made by Reusch and Anderson in IV. Since the one dimethyl group in V also splits into axial and equatorial absorptions when the temperature is lowered it seems fairly certain that the dimethyl group in IV which is not splitting is the one located between the dithioketal groups.

The NMR spectrum of IV at 35° consists of four sharp singlets at 8·92, 8·59, 7·89,

and 6·88 with integrated intensities of 5·6:6·0:3·6:8·0, respectively. These absorptions are assigned to the 5,5-dimethyl, 2,2-dimethyl, ring methylene, and thioketal methylene protons, respectively. Lowering the temperature causes broadening of the singlets at 8·92 and 7·89. Continued lowering of the temperature causes a splitting of the Me absorption at 8·92 into two separate peaks due to the axial and equatorial Me groups with a peak separation of 22 c/s. The methylene singlet becomes a clean AB quartet at the lower temperatures. The spectrum was run repeatedly as the temperature was raised and the coalescence temperature for the Me groups determined to be ca. −66°.

From the coalescence temperature and the max peak separation, $\Delta\nu$, the residence time, $\tau$, was calculated from Eq. (2).[14]

$$\tau = \frac{\sqrt{2}}{2\pi\Delta\nu} \tag{2}$$

The residence time was used to calculate the rate constant for isomerization and the Eyring formulation used to calculate $\Delta F^{\ddagger} = 10{\cdot}4$ kcal/mole at the coalescence temperature.

The NMR spectrum of V at 35° also has four singlets located at 8·90, 8·11, 7·44, and 6·82 with integrated intensities of 5·8, 4·0, 1·8, and 8·0, respectively. These absorptions are assigned to the 5,5-dimethyl, 4,6-methylene, 2-methylene and the dithioketal methylene protons, respectively. The spectrum was taken as the temperature was lowered and the methyl absorption at 8·90 was observed to split into two separate peaks. The coalescence temperature was determined to be ca. −86° and the max peak separation was 17·5 c/s. Using Eq. (2) and the Eyring formulation as before, $\Delta F^{\ddagger}$ for V was calculated to be 9·4 kcal/mole at the coalescence temperature.

## EXPERIMENTAL

M. ps were taken on a Kofler hot stage and are uncorrected. IR spectra were taken on a Perkin–Elmer Infracord Spectrophotometer. NMR spectra were taken on a Varian Associates A-60 or DA-60-EL Spectrometer and were taken in $CS_2$ soln unless otherwise noted.

2,2,5,5-*Tetramethylcyclohexane*-1,3-*dione*. Dimedone (14·0 g, 0·1 mole, Eastman), MeONa (10·8 g, 0·2 mole, Matheson, Coleman and Bell), and 150 ml abs EtOH were placed in a 3-necked, 300 ml flask equipped with a reflux condenser and dropping funnel. A soln of MeI (28·4 g, 0·2 mole, Baker) in 50 ml abs EtOH was added, dropwise, to the refluxing soln. After refluxing for 26 hr the pale yellow soln was stripped of EtOH in a spinning band column. The residue was distilled *in vacuo*. The first fraction, b.p. 95–115° (8 mm) was a wet solid which, on recrystallization from pet. ether (b.p. 30–60°), gave 0·65 g (4%) of a white crystalline solid, m.p. 96–97°, lit.[15] m.p. 98°. The NMR spectrum of this material ($CDCl_3$) consisted of 3 singlets at 7·35, 8·68, and 8·98 with integrated intensities of 4:6·3:5·8, respectively.

*Bis-dithioketal of* 2,2,5,5-*tetramethylcyclohexane*-1,3-*dione* (IV) To a stirred soln of 2,2,5,5-tetramethylcyclohexane-1,3-dione (2·0 g, 0·019 mole) in 1,2-ethanedithiol (6 ml, 0·07 mole) was added 6 ml $BF_3$—etherate (0·046 mole) and stirring continued for 10 min. The reaction was cooled to 0° and 25 ml cold, abs MeOH added. The white ppt which formed was filtered off and washed with cold MeOH, m.p. 162·5–163·5°, lit.[8] m.p. 155–156°, yield 3·11 g (81·7%). The NMR spectrum has 4 singlets at 8·92, 8·57, 7·98, and 6·88 with integrated intensities of 5·6:6·0:3·6:8·0, respectively. The IR showed no CO band.

1.1.4.4-*Tetramethylcyclohexane* (I). A soln of 2,2,5,5-tetramethylcyclohexane-1,3-dione bis-dithioketal (1·25 g, 3·9 mmoles) in 100 ml EtOH was refluxed with 20 g of W-7 Raney Ni catalyst[16]

[14] Ref. 10, p. 223.

[15] T. G. Halsall and D. B. Thomas, *J. Chem. Soc.* 2431 (1956).

[16] Organic Synthesis, Coll. Vol. III, p. 179. John Wiley and Sons, New York (1955).

for 23 hr. The catalyst was filtered off and washed with hot pentane. The combined EtOH and pentane solns were extracted with water and the water layer back-extracted with pentane. The pentane soln was concentrated on a spinning band column and the residue analyzed by GPC. A 20 foot, 10% Dow 710 silicone column at 90° showed the presence of 4 peaks, with one of them major. The major peak was collected, 0·13 g (21%). The NMR spectrum of this material consisted of 2 sharp singlets at 9·15 and 8·78 with integrated intensities of 12·3:8·0, respectively. (Found: C, 85·88; H, 14·5. $C_{16}H_{30}$ requires: C, 85·63; H, 14·4%.)

5,5-*Dimethylcyclohexane*-1,3-*dione bis-dithioketal* (V). To a soln of dimedone (0·42 g, 2 mmoles, Eastman) in 1,2-ethanedithiol (2·4 ml, 28 mmoles, K & K Labs) was added 2·4 ml $BF_3$-etherate (19 mmole, Eastman), and the pale yellow soln stirred for 2 hr at room temp. After adding 10 ml abs MeOH, the soln was stored overnight in the refrigerator. The white needles which formed were filtered off and washed with cold MeOH. After recrystallization from MeOH the white solid had m.p. 178–180°. The NMR spectrum consisted of 4 singlets at 8·90, 8·11, 7·44 and 6·82 with integrated intensities of 5·8:4·0:1·8:8·0, respectively. (Found: C, 49·13; H, 6·86. $C_{13}H_{20}S_4$ requires: C, 49·27; H, 6·89.)

*NMR measurements.* The spectra between −39 and −58° were measured on a Varian A-60 Spectrometer. Those below −58° were measured on a Varian DA-60-EL Spectrometer. The A-60 was equipped with a V-6057 Variable Temperature Probe. With the A-60 spectrometer temp were determined by measuring the peak separation in a MeOH sample. With the DA-60 spectrometer, temps were measured by using a tube containing only solvent with a thermocouple immersed in it. Temp could be controlled to at least ±0·5°. The measurements on I were made on a 3·6% soln in $CS_2$ containing 3·5% TMS and sealed in an NMR tube at atm press. The value for $\Delta\nu$, the max peak separation in I, was obtained at −102°.

Attempts to check the MeOH peak separation temp measuring method against the thermocouple method disclosed a difference between the two methods even in the range −20° to −60° where no extrapolation of the Varian curve is necessary. The difference in this range is fairly constant at 3°. Despite extensive investigation we are unable to give an explanation for this difference. Because the difference is fairly constant its effect on the data is somewhat reduced. It seems reasonable, however, that this problem is responsible for at least a part of the experimental error.

*Acknowledgment*—We wish to thank Dr. E. A. Chandross for helpful suggestions relative to the synthesis of I.