Application of the Forsén–Hoffman Spin-saturation Method and ^{13}C Nuclear Magnetic Resonance Spectroscopy to the Determination of the Barrier to Ring Inversion in *cis*-1,2-, *trans*-1,3-, and *cis*-1,4-Dimethylcyclohexane

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One reason for the inaccuracy of many n.m.r. determinations of activation parameters of exchange is the inaccuracy of rates of exchange determined well away from the coalescence temperature. Such errors can be minimised by using a second method, the Forsén–Hoffman spin-saturation method, to determine accurately the rate of exchange at a considerably lower temperature and by using the greater separation of resonances often found in ^{13}C n.m.r. spectra. This approach is tested on ring inversion of *cis*-1,2-, *trans*-1,3-, and *cis*-1,4-dimethylcyclohexanes.

It is well known that line-shape analysis of n.m.r. spectra of exchanging species leads to accurate values of $\Delta G^{\ddagger}$ close to the coalescence temperature but at temperatures well removed from this temperature, errors arise in the derived values of $\Delta G^{\ddagger}$ which can lead to gross errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.[1] Two approaches are applied in this paper in order to increase the accuracy of such measurements. As shown previously,[2,3] the use of ^{13}C n.m.r. spectroscopy generally increases the separation of the exchanging sites in Hz thus increasing the temperature range over which meaningful exchange rate data can be derived. Unfortunately, systematic errors are still possible in the Arrhenius or Eyring rate law plots. These plots are dominated by the least accurate extreme values, with the plot pivoting about the most accurate data near the coalescence temperature where the rates are generally in the range 100—1 000 s^{-1}. In order to remove such systematic errors, an accurate method is required to determine rates of exchange at temperatures well removed from the coalescence temperature. Such a method based on the Forsén–Hoffman spin saturation method[4] has been recently described.[5] For a two site exchange problem, one site is saturated with a strong radiofrequency magnetic field, while the other site is observed. This method is at its most accurate when the rate of exchange is equal to (spin–lattice relaxation time, $T_1)^{-1}$, *i.e.* generally in the range of 0.1—1 s^{-1} for ^{13}C n.m.r. spectroscopy. Thus by combining this approach with line-shape analysis, it is possible to obtain accurate rates of exchange differing by a factor of 10^3, and consequently derive accurate values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. In the initial experiments, the method was applied to *cis*-decalin,[5] and it was found that $\Delta H^{\ddagger} = 12.35 \pm 0.11$ kcal mol^{-1} and $\Delta S^{\ddagger} = +0.15 \pm 0.44$ cal K^{-1} mol^{-1} in contrast to the previously reported values of $\Delta H^{\ddagger} = 13.6$ kcal mol^{-1}, and $\Delta S^{\ddagger} = +3.3$ cal K^{-1} mol^{-1}.[3] These discrepancies were explicable, but in order to establish the method further, it has been applied to the inversion of the dimethylcyclohexanes.

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EXPERIMENTAL

The mixtures of *cis*- and *trans*-1,2-, -1,3-, and -1,4-dimethylcyclohexanes were separated by g.l.c. using a Pye 105 automatic preparative chromatograph to give *cis*-1,2-, *trans*-1,3-, and *cis*-1,4-dimethylcyclohexane. In each case a *ca.* 45% (v/v) solution in CD_2Cl_2 or CD_2Cl_2–CH_2Cl_2 was prepared. The experimental procedure has been described previously.[5] One difference in procedure is that a 2 000 Hz spectral width was used for some of the measurements, giving a potential resolution of 0.48 Hz.

RESULTS AND DISCUSSION

It has been shown previously [4,5] that in the case of exchange between two equally populated sites, *A* and *B*, when a strong radiofrequency field is applied at site *B* at time $t = 0$, then the magnetisation at site *A* decreases from an initial value of $M_z^A(0)$ to a value $M_z^A(t)$ after a time *t*, and when $t \longrightarrow \infty$ equation (1)

$$\tau_A = \{M_z^A(\infty)/[M_z^A(0) - M_z^A(\infty)]\}T_{1A} \qquad (1)$$

applies where τ_A is the average lifetime in site *A* and T_{1A} is the spin–lattice relaxation time at site *A*. $M_z^A(0)$ and $M_z^A(\infty)$ can be measured in the absence and presence, respectively, of a strong radiofrequency field at site *B* provided that there is at least $5(\tau_A^{-1} + T_{1A}^{-1})^{-1}$ between switching off or on the irradiating field and commencing the measurement. T_{1A} can be measured using the conventional $(T_d–\pi–\tau–\pi/2)_n$ pulse sequence provided that $T_{1A} = T_{1B}$ within experimental error. If $T_{1A} \neq T_{1B}$ then the value obtained for T_{1A} will be inaccurate.[6] Fortunately, in the cases of *cis*-1,2-, *trans*-1,3-, and *cis*-1,4-dimethylcyclohexane, $T_{1A} = T_{1B}$ for each pair of exchanging carbon atoms and consequently τ_A can be calculated using equation (1). A typical ^{13}C n.m.r. spectrum for *cis*-1,4-dimethylcyclohexane at —90 °C is shown in Figure 1a. When one methyl carbon atom is subjected to a strong radiofrequency field, the magnetisation of the other methyl carbon atom is strongly reduced (see Figure 1b). The experiment was repeated irradiating each exchanging carbon atom in turn, but it was not possible to perform the experiment reliably when the two exchanging sites are closer than 50 Hz, while great care is necessary to obtain complete saturation of one line without partially saturating the second site when the separation is between 50 and 100 Hz. At least four rates were determined at each temperature, *e.g.* to give a scatter of 0.381, 0.422, 0.476, and 0.483 s^{-1} in a good case (*cis*-1,4-dimethylcyclohexane at —98.5 °C) to 0.95, 1.09, 1.15, 1.31, 1.615, 1.79, and 2.18 s^{-1} in a bad case (*trans*-1,3-dimethylcyclohexane at —96 °C), and in each case these values were averaged.

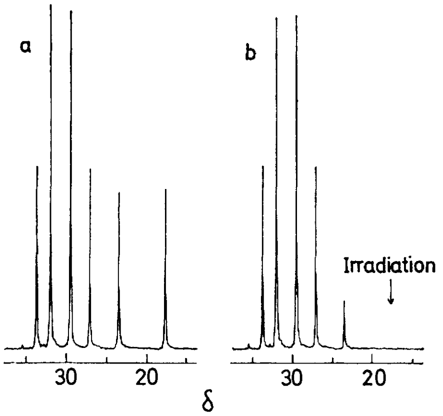

FIGURE 1 a, The ^{13}C n.m.r. spectrum of *cis*-1,4-dimethylcyclohexane in CD_2Cl_2–CH_2Cl_2 at -90 °C; b, as a but with a strong radiofrequency field at δ 18

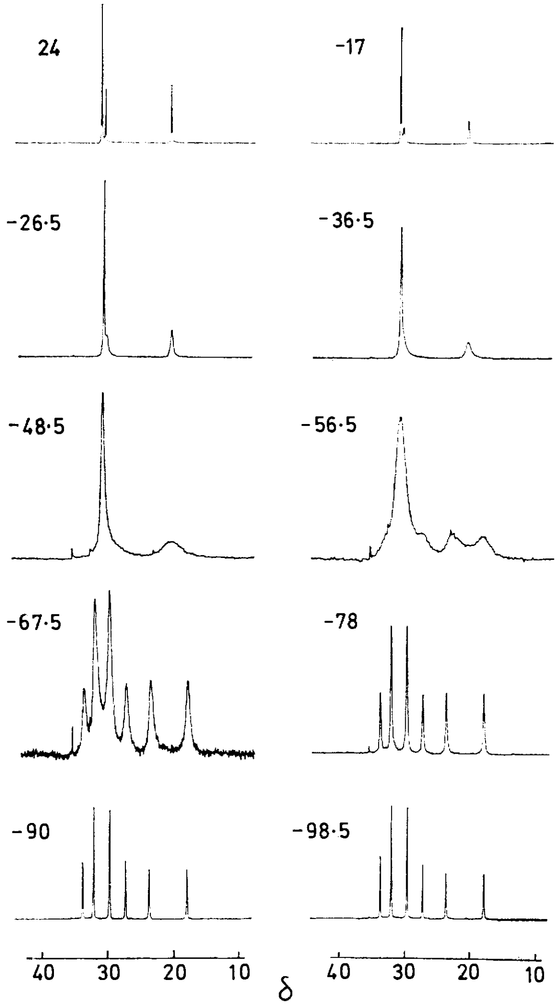

FIGURE 2 The variable temperature ^{13}C n.m.r. spectra of *cis*-1,4-dimethylcyclohexane in CD_2Cl_2–CH_2Cl_2. There are also weak signals present due to a small quantity of the *trans*-isomer

At higher temperatures, total line shape analysis was used, and a typical set of spectra are given in Figure 2. Line-shape analysis is subject to a number of errors. Often in ^1H n.m.r. spectroscopy, the exchanging resonances are close together, and any change in position with temperature can produce gross errors.[1] In the case of this ^{13}C n.m.r. investigation, no evidence was found for significant (>2 Hz) changes in the line positions

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with temperature. Such a temperature variation in chemical shift is small compared to the greatest shift differences for each compound (134.5—229 Hz). An error in line position will only give errors in the calculated rate near and above the coalescence temperature and such errors will be small, *i.e.* <3% in the rate. A more severe source of error is the determination of the line-width in the absence of exchange. In the case of *trans*-1,3-dimethylcyclohexane, the C-2 and -5 signals were used as a monitor of the line-width in the absence of exchange. In the other cases, the CH_2Cl_2 and/or tetramethylsilane signal(s) were used as a line-width monitor. This procedure can introduce errors but the line-widths of the reference signals and the remainder of the signals were equal for both the limiting low temperature spectra and the limiting high temperature spectra. Only spectra where the exchange broadened lines are broader than three times the width of the reference line were used to calculate the rate. An error in the line-width in the absence of exchange will cause a systematic error in the calculated activation parameters. If the line-width in the absence of exchange is over-estimated, then the rate below coalescence will be under-estimated and over-estimated above coalescence causing E_a, $\Delta H^\ddagger$, and $\Delta S^\ddagger$ to be more positive by an amount which will not be shown by the conventional least-squares analysis. If the line-width in the absence of exchange is under-estimated, then the converse will be true. These errors are very difficult to detect in a normal line-shape analysis. The use of spin-saturation measurements to determine very slow rates combined with line-shape analysis near coalescence permits an accurate determination of the Arrhenius or Eyring plot and thus shows up such errors if they are occurring. The use of 10 mm n.m.r. tubes for ^{13}C n.m.r. spectroscopy does increase the error in temperature control. Thermocouple measurements show that there can be up to a 1 °C temperature gradient over even a short (12 mm) sample. Over the 80 °C range used in these measurements, such temperature errors, which may not be random, can only produce a small error. It is therefore reasonable to take the least squares errors as a good estimate of the accuracy of the measurements. The Eyring rate plot for *cis*-1,4-dimethylcyclohexane is shown in Figure 3, and the rate data for all three compounds are given in Table 1. Following the practice adopted by previous workers, a value of 0.5 has been used for κ in the Eyring rate equation (2). The thermodynamic parameters are given in Table 2.

TABLE 1

Experimentally determined rates of inversion at various temperatures for *cis*-1,2-, *trans*-1,3-, and *cis*-1,4-dimethylcyclohexane in dichloromethane solution

T/K	k/s^{-1}	T/K	k/s^{-1}	T/K	k/s^{-1}
cis-1,2-Dimethylcyclohexane					
177	0.68 [a]	211	80 [b]	253.5	6 600 [b]
186	3.7 [a]	221.5	375 [b]	263.5	14 800 [b]
199	26 [b]	232.5	1 300 [d]	272.5	25 000 [b]
202	34 [b]	242.5	2 500 [b]		
trans-1,3-Dimethylcyclohexane					
174.5	0.79 [a]	205.2	105 [b]	236.2	2 900 [b]
186.2	3.13 [a]	219.2	392 [b]	246.7	6 000 [b]
195.2	19.8 [b]	228.2	920 [b]		
cis-1,4-Dimethylcyclohexane					
174.7	0.429 [a]	205.7	51.8 [b]	236.7	1 675 [b]
183.2	1.96 [a]	216.7	173 [b]	246.7	4 900 [d]
195.2	10.4 [b]	224.7	454 [b]	256.2	8 850 [b]

[a] Measured using the Forsén–Hoffman spin-saturation method. [b] Measured using line-shape analysis.

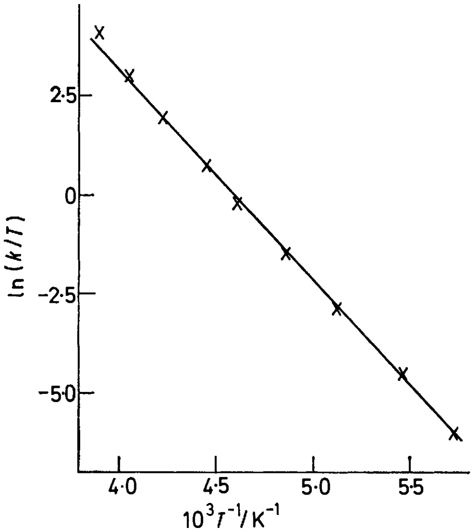

FIGURE 3 The Eyring rate plot for *cis*-1,4-dimethylcyclohexane in CD_2Cl_2–CH_2Cl_2

TABLE 2

Activation parameters for ring inversion in cyclohexane, *cis*-1,2-, *trans*-1,3-, and *cis*-1,4-dimethylcyclohexane. The errors quoted are one standard deviation as determined using regression analysis. $\Delta G_{300}^\ddagger$ is calculated using the $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values given here

Compound	$\Delta H^\ddagger$/ kcal mol^{-1}	$\Delta S^\ddagger$/ cal mol^{-1} K^{-1}	$\log_{10}A$	E_a/ kcal mol^{-1}	$\Delta G_{300}^\ddagger$/ kcal mol^{-1}
Cyclohexane [a]	10.71 ± 0.04	+2.2 ± 0.2			10.05
cis-1,2-Dimethylcyclohexane	10.11 ± 0.15	+0.6 ± 0.7	12.93 ± 0.14	10.54 ± 0.14	9.93
trans-1,3-Dimethylcyclohexane	10.48 ± 0.33	+3.1 ± 1.6	13.77 ± 0.35	10.98 ± 0.33	9.55
cis-1,4-Dimethylcyclohexane	10.54 ± 0.10	+2.5 ± 0.5	13.31 ± 0.11	10.95 ± 0.11	9.79

[a] Data taken from ref. 7.

$$\text{rate} = \kappa(kT/h)\exp(\Delta S^\ddagger/R)\exp(-\Delta H^\ddagger/RT) \quad (2)$$

The values obtained for $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for *cis*-1,2-, *trans*-1,3-, and *cis*-1,4-dimethylcyclohexane are a little different from the previously published data, but the differences lie within the quoted standard deviations. However, the direction of the changes are such that now the activation parameters for *cis*-1,2-dimethylcyclohexane are much closer to those for cyclohexane[7] (see Table 2). This result is surprising as the compound should be significantly destabilised by non-bonded interactions not present in cyclohexane. It thus appears probable that these interactions do not markedly change in the transition state. It is clear that high quality calculations, such as those on cyclohexane are required in order to understand the interactions.[8]

In conclusion, the use of spin-saturation in addition to line-shape analysis enables the determination of more accurate and more reliable $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values than line-shape analysis on its own.

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