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ON THE MECHANISM OF CONFORMATIONAL INTERCONVERSION IN CYCLOHEXENE DERIVATIVES

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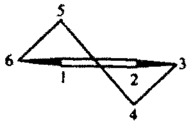
Abstract—The free energy barriers to ring inversion for 3,3-dimethylcyclohexene, 4,4-dimethylcyclohexene and 3,3,6,6-tetramethylcyclohexene were determined by low temperature PMR studies. The results were interpreted in terms of a mechanism whereby the boat conformation is of highest energy on the energy profile for conformational interconversion. The very high ΔG^{*} value for 3,3,6,6-tetramethylcyclohexane (8·4 kcal/mole) is considered a reflection of the serious non bonded interaction that exists between methyl groups at the "prow" positions of the boat form.

Cyclohexene is a fundamental structural unit of a large number of important complex molecules and, although several important studies[1-8] have been concerned with the interconversion of its half-chair (1) conformation, the exact nature of the inversion mechanism is still of current interest.[4,5] The main investigative approaches were concerned with various conformational energy calculations and spectroscopic data.

Having at first predicted different mechanisms, the various sets of recent calculations that have been reported, now appear to agree with each other. A synthesis of the earlier results reveals that the two models put forward were concerned with determining whether the inversion pathway contained a metastable boat (2) intermediate[3] or whether, as is now accepted, this form is actually the maximum energy conformation[1,2,5] on the energy profile of conformational interconversion.



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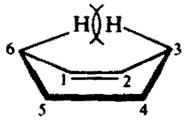

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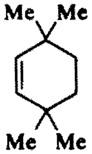
On the other hand, the pertinent experimental results published were obtained from NMR investigations on substituted cyclohexene derivatives. For example, Anderson and Roberts[6] have reported that perfluorocyclohexene has a free energy barrier about 1·5 kcal/mole higher than cyclohexene[7] while Jensen and Bushweller[8] studied derivatives containing one or two substituents on carbons 4 and 5 of the cyclohexene ring. From arguments based on an increase in torsional energy due to eclipsing about the C_4—C_5 bond, these authors favoured the boat transition state, although they were careful to point out that their interpretation was not completely free from criticism since it is not at all certain that partial eclipsing as would exist in another transition state might not be sufficient to raise its energy above that of the boat which would then become a metastable intermediate.

Since our knowledge of the inversion mechanism of cyclohexene relies heavily on calculations which cannot be rigorously supported or rejected by the limited quantity of reliable experimental data available, we have chosen to investigate this problem through a consideration of substituent effects mainly at position 3 of the cyclohexene ring. For this purpose we have prepared 3,3,6,6-tetramethylcyclohexene (3), 3,3-dimethylcyclohexene (4) and 4,4-dimethylcyclohexene (5). This choice of compounds was guided by the desire to bring out the effects of the transannular "prow-prow" interaction in the boat (2) form, if indeed it is the conformation of the transition state.



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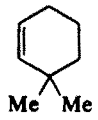

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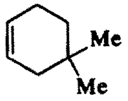

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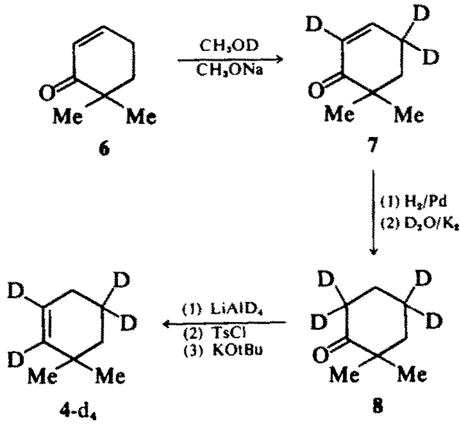
RESULTS

The compounds investigated were prepared by standard reactions on known ketone precursors. Compound 3 was prepared from 2,2,5,5-tetramethylcyclohexanone[9] by formation of the tosylhydrazone and subsequent elimination with n-butyl lithium.[10] Compound 5 was prepared similarly from 4,4-dimethylcyclohexanone.[11] For reasons described later, our study required the preparation of a deuterated derivative of 4, namely 3,3-dimethyl-1,2,5,5-tetradeuteriocyclohexene (4-d_4) by a somewhat elaborate route as is summarized in Scheme 1. The first reaction consisted of the base catalyzed exchange[12] of the labile protons of 6,6-dimethyl-



SCHEME 1

cyclohexenone[13] (**6**) to give the trideuterated derivative **7** whose double bond was then reduced. Base catalysed exchange of the saturated ketone with deuterium oxide produced the tetradeuterated derivative **8** which was reduced to the alcohol, followed by tosylation and elimination to yield the desired deuterated derivative **4**-d$_4$. These compounds were then submitted to a complete PMR study at variable temperature.

The upfield portion of the room temperature PMR spectrum at 100 MHz of 3,3,6,6-tetramethylcyclohexene (**3**) dissolved in a mixture of vinyl chloride and chlorodifluoromethane (85:15) contains a singlet at δ 0·957 (four Me groups) and a signal centered at δ 1·485 (two methylene groups). As the temperature is decreased the spectrum undergoes a change such that at −125° the Me signal has split into a doublet separated by 3·4 Hz (coalescence temperature, $T_c = -115°$) whereas the signal centered at δ 1·485 has changed into an unresolved multiplet resembling an AA′BB′ pattern.[14] Fig 1 illustrates the gradual spectral change just described together with a series of theoretical spectra of the methyl signal for various values of the rate constant (k) generated by a computer and CALCOMP plotter utilising the procedure described below.

The PMR spectrum of the methyl region of 4,4-dimethylcyclohexene (**5**) in the chlorodifluoromethane showed a change from a singlet to a doublet separated by 9·2 Hz below the coalescence temperature of −152°. A computer simulation of this spectral change was also carried out.

The rate constants (k) characterising the broadened spectra of compounds **3** and **5** were obtained from a least-square comparison of experimental and computer calculated spectra of the Me region by means of a modified version of Saunder's program.[15] Since, at these very low temperature, T_2 could not be obtained accurately from an unchanged spectral line belonging to the molecule[16] and sufficiently low temperatures could not be reached to get an accurate value for the chemical shift difference ($\Delta\nu$) of the Me doublet of **5**, our procedure involved a systematic variation of T_2 and $\Delta\nu$ until a best fit was obtained through iteration on k for each set of values. The uncertainty in T_2, the very small $\Delta\nu$ for **3** and the small and approximate $\Delta\nu$ for **5** preclude a calculation of reliable $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and only justify the calculation of $\Delta G^{\neq}$.[16]

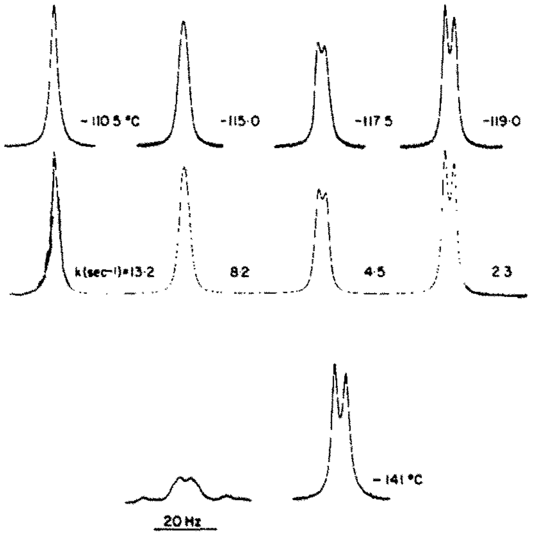


Fig 1. The 100 MHz PMR spectra of compound **3**. Top: Experimental spectra of the Me protons at the indicated temps: Centre: Calculated spectra; Bottom: Experimental spectrum of the methylene and methyl protons at −141°.

The free energy of activation ($\Delta G^{\neq}$) was obtained from the Eyring equation in the usual manner[17] using a transmission coefficient of one. A summary of these values is given in Table 1 for simulations carried out at the temperature $T^{\neq}$ usually a few degrees below T_c. The values reported in this table are within 0·2 kcal/mole of those estimated from approximate equations for k at T_c.[18]

The room temperature deuterium decoupled 100 MHz PMR spectrum of 3,3-dimethyl-1,2,5,5-tetradeuteriocyclohexene (**4**-d$_4$) dissolved in chlorodifluoromethane contains three singlets: one at δ 0·972 (two Me groups), another at δ 1·468 (methylene group at position 4) and the last one at δ 1·917 (methylene group at position 6). As the temperature is lowered only the signal at δ 1·468 changes its appearance from a singlet to an AB quartet. The other two signals remain as singlets down to −170°, the lowest temperature accessible. The coalescence temperature for this change was estimated at −141° and the analysis of the AB at −165° gave a chemical shift difference of 20·8 Hz and a coupling constant equal to −13·0 Hz. It is interesting to note that the spectra of the undeuterated analog (**4**) just barely revealed an undefinable spectral change in a very complex multiplet. The deuterated derivative

Table 1. Free energies of activation ($\Delta G^{\neq}$) for the conformational interconversion of cyclohexene and some of its derivatives

Compound	$T^{\neq}$ (T_c) °C[a]	$\Delta G^{\neq}$, kcal/mole	$\Delta\Delta G^{\neq}$
3	−117·5 (−115)	8·4[b]	3·1
4-d$_4$	−146·8 (−141)	6·3[b]	1·0
5	−155·8 (−152)	6·1[b]	0·8
cyclohexene[c]	(−164)	5·3	0·0

[a] Error in $T^{\neq}$ is ±0·5°; error in T_c is ±2°.
[b] Error in $\Delta G^{\neq}$ at $T^{\neq}$ is ±0·2.
[c] Data taken from ref. 7.

4-d$_4$ is therefore essential to a meaningful analysis of the spectral modification.

Fig 2 shows the experimental spectra of **4-d$_4$** at various temperatures together with a "best fit" computer calculated spectrum using a procedure similar to that employed for **3** and **5** based on a computer program written from the equations of an exchanging AB as reported by Whitesides *et al.*[19] The $\Delta G^{\neq}$ value was calculated as previously described and is reported in Table 1.

DISCUSSION

The low temperature PMR spectra of compounds **3**, **4-d$_4$** and **5** are in accord with half-chair conformations, possibly slightly deformed from that of cyclohexene,[20] for each molecule. Only 3,3,6,6-tetramethylcyclohexene retains the twofold axis of symmetry through the C_1—C_2 and C_4—C_5 bonds, and as a consequence the pattern observed for the signal of the methylene protons is of the AA′BB′ type (Fig 1). A complete analysis of this spectrum, which would have provided information about dihedral angles, was not possible because the number of lines observed clearly is too small for a meaningful iterative computer simulation.

Limitations inherent to the dynamic NMR method[16] preclude the experimental determination of $\Delta S^{\neq}$ and consequently of $\Delta H^{\neq}$ for all three molecules. On the other hand, it has often been suggested that for non polar molecules, the entropy of activation turns out to be essentially equal to that calculated from symmetry considerations.[6–8, 21] The expected $\Delta S^{\neq}$ values calculated thusly yield small positive numbers which contribute only slightly to $\Delta G^{\neq}$. It therefore seems apparent that entropy effects on differences of $\Delta G^{\neq}$ ($\Delta\Delta G^{\neq}$ in Table 1) for any compound relative to cyclohexene will be within experimental errors. The approximation $\Delta\Delta H^{\neq} \approx \Delta\Delta G^{\neq}$ is therefore valid under the present circumstances; this parameter will find use later in correlations of substituent effects.

Having at first predicted different energy profiles for ring inversion of cyclohexene, revised calculations[5] now unanimously suggest that the boat is the conformation of maximum energy adopted transiently by the molecules as they invert. Our approach will then consist in the investigation of the compatibility of this theoretical model with our experimental results.

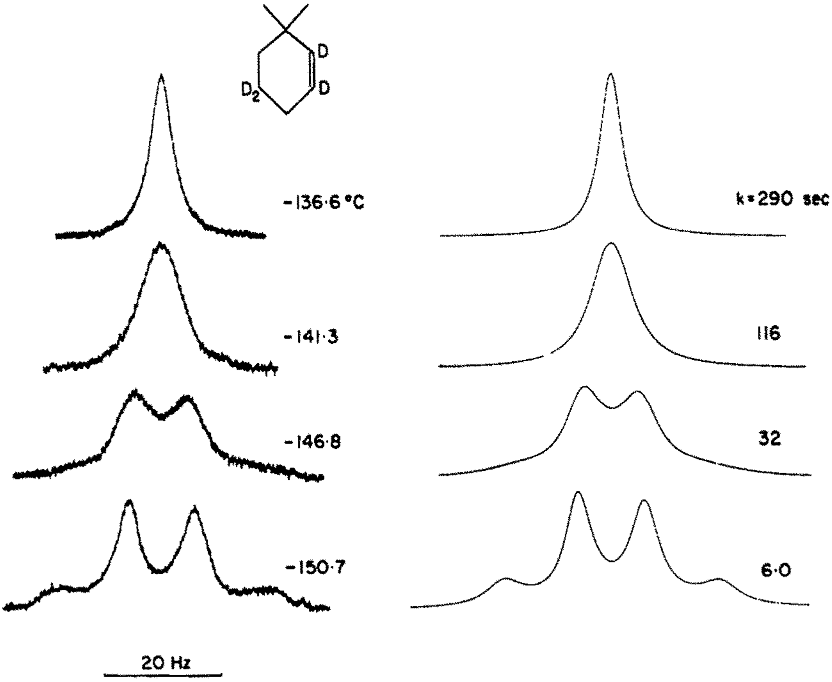
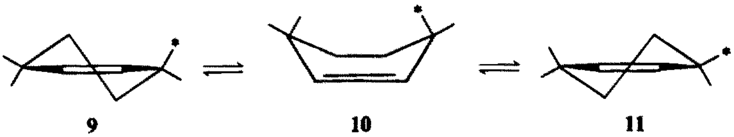


Fig 2. Experimental (100 MHz, deuterium decoupled) of compound 4-d$_4$ at the indicated temps. and calculated PMR spectra of the C-4 methylene protons.

An examination of the features of the boat conformation illustrated by structure **2** suggests that substituting the interior protons ("prow" protons) by bulky groups should lead to a significant "prow-prow" interaction as the substituents come within each other's van der Waals radii. 3,3,6,6-Tetramethylcyclohexene, whose interconversion mechanism is drawn below ($9 \rightleftharpoons 10 \rightleftharpoons 11$), satisfies this condition. Structure **10** shows that two methyl groups must come very close together when the molecules adopt the boat conformation. This serious nonbonded interaction undoubtedly makes the energy of this form the highest on the interconversion profile. Hence the relatively large $\Delta\Delta G^{\neq}$ value of 3·1 kcal/mole (or alternatively $\Delta G^{\neq} = 8{\cdot}4$ kcal/mole, the highest known for a derivative of cyclohexene) determined for **3** is satisfactorily explained by the proposed theoretical model.

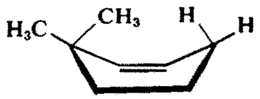
The examination of Dreiding models for the cyclohexane chair and the cyclohexene boat reveals that comparable distances separate the 1,3-axial protons of the chair and the 1,4 "prow" protons of the boat (i.e. 2·5 Å and 2·4 Å respectively). Since calculations[24] have shown that most of the energy of the 1,3-axial methyl-proton interaction results from nonbonded repulsive forces, the experimental results reported previously for **13** and **14** represent fair approximations for the similar interactions found in the boats **10** and **12**.

Thus the ratio of 3 observed for the relative weight of the $\Delta\Delta G^{\neq}$ values for **3** and **4** is sufficiently close to the experimental ratio of 4 determined for **13** and **14** to suggest that the nonbonded interaction in the boat forms is a major contributor to the differences in barriers to ring inversion as is intuitively predicted from the proposed theoretical model.



9 **10** **11**

3,3-Dimethylcyclohexene (**4** or $\mathbf{4\text{-}d_4}$) is characterized by a $\Delta\Delta G^{\neq}$ value of 1·0 kcal/mole. A comparison of this value with that of **3** reveals a lack of additivity for the effect of successive substitution of gem-dimethyl groups at the allylic positions of cyclohexene. Although this non-additivity could conceivably be the result of a superposition of several subtle effects, it appears intuitively to be due in large part to a change in nonbonded interaction between the groups at the "prow" position of the boat form, if the theoretical model holds.



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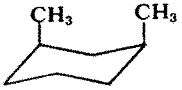

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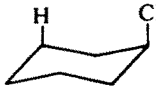
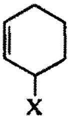


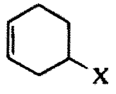
14

Evidence that the "prow-prow" interaction is a major contribution to the $\Delta\Delta G^{\neq}$ values of **3** and **4** follows from a close scrutiny of a more familiar system, namely the cyclohexane chair with one or two methyl groups at the 1,3-axial positions as depicted by structures **13** and **14**. Equilibration experiments[22,23] have revealed that the energy of a methyl–methyl interaction such as in **13** is about 3·7 kcal/mole, whereas that for a methyl–proton repulsion as in **14** is about 0·9 kcal/mole. Thus a ratio of 4 weighs the relative importance of these two types of interactions.

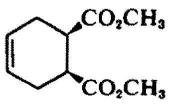
The comparative analysis of the $\Delta\Delta G^{\neq}$ values for 3,3-dimethylcyclohexene and 4,4-dimethylcyclohexene (**5**) is not as straightforward since a close examination of models for both half-chair conformations shows that it is extremely difficult to distinguish between steric and torsional effects. The close structural features of these two compounds and the essentially identical inversion barriers suggest that both molecules probably invert by the same mechanism. It would then appear that the predominant contribution to the $\Delta\Delta G^{\neq}$ value determined for **5** arises from increased torsional energy in the transition state as already suggested[6,8] for several substituted derivatives of cyclohexene at position 4.



15a: X = Br
15b: X = CH$_3$



16a: X = Cl
X = Br
X = I



17

A previous PMR investigation[8] was concerned with compounds **15**, **16** and **17**. The experiments for both **15a** and **15b**, which contain a substituent at position 3 as do derivatives **3** and **4**, were inconclusive because of the failure to observe a spectral change down to about −170°. This behaviour was attributed to a very small chemical shift difference for the H—C—X resonances. This interpretation is apparently supported by the analysis of the spectrum of $4\text{-}d_4$ at −170° which shows that the chemical shift difference between the two nonequivalent methylene protons on C_6 is very small (A_2 pattern) whereas it is about 21 Hz for the methylene protons on C_4 (AB quartet in Fig 2). On the other hand, spectral changes were observed for **16** and **17** and $\Delta G^{\neq}$ barriers turned out to be between 6·3 and 7·4 kcal/mole. The larger value being characteristic of **17** is significantly higher than cyclohexene and only slightly lower than that of **3**. Eclipsing of the two carbomethoxy groups in a boat transition state has been invoked to explain this particular $\Delta G^{\neq}$ value.

Although a quantitative interpretation of all experimental results is not possible at the present, since it would require a breakdown of the energy barrier into various ill-defined terms each contributing partially to the overall substituent effect on $\Delta\Delta G^{\neq}$, the complementary aspect of all results is significant.

It is apparent from our conclusion and earlier thoughts[8] that the experimental results available so far support the inversion mechanism proposed on theoretical grounds. Furthermore we believe that the strength of the theoretical method could be significantly enhanced through calculations of the energy barriers for compounds **3** and **4** using the same set of postulates as used for cyclohexene. Successful tests of the calculations with three experimental values would certainly argue more convincingly in favour of the underlying inversion mechanism.

EXPERIMENTAL

The VPC analyses and separations were carried out on a Varian-aerograph A90-P3 instrument using ¼ in. columns and helium as carrier gas. Mass spectral analyses were performed on an Associated Electrical Industries model MS-902 mass spectrometer operating at 12 and 70 eV.

Routine analytical PMR spectra were recorded on a JEOL C-60H spectrometer operating at 60 MHz in the external lock mode. The low temperature PMR spectra were obtained at 100 MHz using a JEOL JNM-4H-100 spectrometer. Solutions in vinyl chloride and/or chlorodifluoromethane (as specified) containing a small quantity of TMS were degassed and sealed. Deuterium decoupling, when required, was effected by means of the JEOL Hetero Spin Decoupler model JNM-SD-HC.

Temperatures were monitored by means of a JEOL temperature control unit model JES-VT-3 and determined accurately with a calibrated thermocouple placed inside a solvent-containing dummy NMR tube. Temperature measurements were taken before and after recording several PMR spectra at each reported temperature. A variation of less than 0·5° was ordinarily observed between the two sets of temperature readings.

Rate constants were obtained from an iterative comparison of experimental and computer calculated spectra. For this purpose, 5 to 8 spectra were recorded at a sweep rate of 0·15 Hz/sec without saturation at each temp. The region of interest was digitized manually taking from 50 to 120 experimental points which provided the basis for iterative adjustment of the experimental and theoretical spectra calculated, using programs identified in the text, on either a CDC 6600 or CDC CYBER 74 computer and then traced by means of a CALCOMP plotter.

3,3,6,6-*Tetramethylcyclohexene* (**3**). This compound was prepared by a reaction described recently[10] from 2,2,5,5-tetramethylcyclhexanone[9] (1·54 g; 0·010 mole) and *p*-toluenesulfonylhydrazine (1·86 g; 0·010 mole). Reaction of the precipitated tosylhydrazone (2·68 g) with 1·5 M n-BuLi provided a product obtained pure by preparative VPC using a DC 550 (15%, 5 ft) column at 90°. The PMR spectrum of the compound was identical to that reported for 3,3,6,6-tetramethylcyclohexene prepared by a different route.[25]

3,3-*Dimethyl*-1,2,5,5-*tetradeuteriocyclohexene* (**4**-d_4). Base catalyzed deuteration[12] of **6**[13] (2·5 g; 0·020 mole), using a soln of 34 g of methanol-OD, 5 g of D_2O and 0·45 g of Na, yielded **7** whose structure is verified by its PMR spectrum in CCl_4 at 100 MHz with deuterium decoupling: 1·05 ppm (s, two Me), 1·78 ppm (s, CH_2 at position 5), 6·7 ppm (s, olefinic proton on C-3).

All of compound **7** was then hydrogenated in EtOAc in the presence of 0·45 g of Pd-C (10%) under 2·2 atm pressure. VPC analysis using a carbowax 20 M column at 160° showed a single peak characterized by a retention time identical to authentic 2,2-dimethylcyclohexanone. Preparative VPC afforded 0·62 g of the deuterated ketone whose PMR spectrum showed an absence of signals characteristic of olefinic protons.

The isolated ketone was then stirred for 2 hr with 15 ml of D_2O containing 1·5 g of K_2CO_3. The product was then extracted with CCl_4; the soln was dried with $MgSO_4$ and then distilled in a micro apparatus. The 100 MHz, room temp, deuterium decoupled PMR spectrum of a 3% soln of this ketone dissolved in CHF_2Cl shows the following signals in accord with that expected for **8**: 1·10 ppm (s, two Me), 1·66 ppm (CH_2 on C-5) and 1·81 ppm (CH_2 on C-3). The following isotopic composition was calculated from the mass spectrum at low ionization potential obtained from a Hitachi Model RMU-6 spectrometer: $d_4 = 66\%$, $d_3 = 28\%$, $d_2 = 5\%$, $d_1 = 1\%$.

Compound **8** was then dissolved in 5 ml of anhyd ether and added dropwise to a suspension of 0·10 g of LAD_4 in 5 ml ether. After 1 hr of stirring, the soln is neutralized with 6 M H_2SO_4. The organic phase is separated, washed with sat $NaHCO_3$ aq and then dried over $MgSO_4$. After evaporation of the solvent, VPC analysis (carbowax 20 M, 20%) showed that the starting ketone had disappeared. This crude product was then dissolved in 5 ml of pyridine containing 0·850 g of *p*-toluenesulfonyl chloride (freshly crystallized from light petroleum). The soln was left standing for 24 hr at 0° followed by the addition of 20 ml water. The product was extracted with ether; the organic phase was washed successively with 6 N HCl, water, and then dried over $MgSO_4$.

Most of the ether was evaporated from the above tosylate which was then dissolved in anhyd DMSO to which was added 2·25 g of t-BuOK (Alfa Inorganics). The elimination reaction was carried out according to a published procedure.[26] After work up, the product was isolated by preparative VPC using a 20% carbowax 20 M column at 90° and identified as compound **4**-d_4 from the following analytical data: The 100 MHz, room temp, deuterium decoupled, PMR spectrum of a 3% soln in CHF_2Cl given in the text (Fig 2). (Anal. Calcd. for $C_8H_{10}D_4$: mol. wt. 114·1346. Found: 114·1348, mass spectrum at 70 eV).

4,4-*Dimethylcyclohexene* (**5**). This compound was prepared from 4,4-dimethylcyclohenanone[11] (2·52 g; 0·020 mole) by the procedure already described for **3**. The product, purified by VPC, dissolved in CHF_2Cl, gave a PMR spectrum at room temp in agreement with the proposed structure **5**: 0·826 ppm (s; two CH_3), 1·38 ppm (tr with

$J = 6{\cdot}3$ Hz; CH_2 at C-5), 1·80 ppm (s, CH_2 at C-3), 2·05 ppm (m, CH_2 at C-6) and 5·6 ppm (broad s, olifinic protons). (Anal. Calcd. for C_8H_{14}: mol. wt. 110·1095. Found: 110·1095, mass spectrum at 70 eV).

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