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CONFORMATIONAL ANALYSIS BY NUCLEAR MAGNETIC RESONANCE—VII

THE CONFORMATIONAL FREE ENERGY OF THE NITRO GROUP

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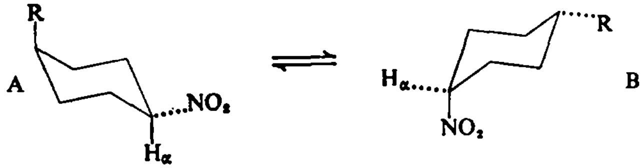
Abstract—The conformational equilibria of nitrocyclohexane and *cis*-4-methylnitrocyclohexane have been investigated by NMR. The equilibrium constants for both compounds have been calculated from the band widths and time averaged coupling constants of the α-proton at room temperature, whilst low temperature studies have been carried out on *cis*-4-methylnitrocyclohexane. From these measurements, the conformational free energy (ΔG value) of the nitro group has been found to be 1·3 kcal/mole.

IN A preliminary communication,[1] it was reported that the conformational free energy of the nitro group (ΔG value) was approximately 1 kcal/mole, and that nitrocyclohexane (I) existed at room temperature to 85% in conformer I_A (Fig. 1). The original investigation was instigated in view of the report[2] that nitrocyclohexane existed solely in conformer I_A, with a fixed equatorial nitro group. In order to improve the accuracy of the method, as it had been shown that the equilibrium constant K for the equilibrium $I_A \rightleftharpoons I_B$ was 5·7,[1] it was thought desirable to synthesize a disubstituted derivative, in which the equilibrium constant was closer to 1. To this end *cis*-4-methylnitrocyclohexane has been prepared, and this paper will describe the NMR spectra of this compound and nitrocyclohexane, together with the spectra *cis*- and *trans*-4-t-butylnitrocyclohexane, which were used as standards in the NMR analysis; the NMR spectra of these four compounds have been determined at 60 Mc/s and 100 Mc/s, and the results are set out in Table 1.



I Nitrocyclohexane R = H.
II *cis*-4-Methylnitrocyclohexane R = CH_3.

FIG. 1. The two most stable conformers of nitrocyclohexane (I) and *cis*-4-methylnitrocyclohexane (II).

From these measurements it has been possible to apply some of the methods of conformational analysis by NMR as recently discussed in a review article, and the nomenclature as explained in this review article has been used here.[3]

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[1] H. Feltkamp and N. C. Franklin, *J. Amer. Chem. Soc.* **87**, 1616 (1965).

[2] W. Hofman, L. Stefaniak, T. Urbanski and M. Witanowski, *J. Amer. Chem. Soc.* **86**, 554 (1964).

[3] H. Feltkamp and N. C. Franklin, *Angew. Chem.* **77**, 798 (1965); *Angew. Chem.* (Internat. Edit.) **4**, 774 (1965).

TABLE 1. SUMMARY OF THE NMR DATA

			α-proton		Coupling constants (in c/s)			
	Mc/s	Solvent	Chemical shift	Bandwidth (in c/s)	J_{aa}	J_{ae}	J_{ea}	J_{ee}
Nitrocyclohexane	60	$CDCl_3$	5·59 τ	27·2				
Nitrocyclohexane	100	$CDCl_3$	5·62 τ	29·0	10·35	4·20		
cis-4-t-Butyl-nitrocyclohexane	60	$CDCl_3$	5·47 τ	13·0				
cis-4-t-Butyl-nitrocyclohexane	100	$CDCl_3$	5·50 τ	13·0			4·20	2·40
cis-4-t-Butyl-nitrocyclohexane	100	CS_2	5·63 τ	12·5				
trans-4-t-Butyl-nitrocyclohexane	60	$CDCl_3$	5·69 τ	31·0	11·5	4·0		
trans- 4-t-Butyl-nitrocyclohexane	100	$CDCl_3$	5·69 τ	31·1	11·55	4·03		
trans-4-t-Butyl-nitrocyclohexane	100	CS_2	5·86 τ	31·0	11·5	4·0		
cis-4-Methyl-nitrocyclohexane	60	$CDCl_3$	5·53 τ	19·0				
cis-4-Methyl-nitrocyclohexane	100	$CDCl_3$	5·53 τ	19·2				
cis-4-Methyl-nitrocyclohexane (at 25°)	100	CS_2	5·70 τ	19·0				
cis-4-Methyl-nitrocyclohexane (at −80°)	100	CS_2	5·63 τ_e 5·82 τ_a	13·0 —				

There was little value in applying the method of analysis based on the chemical shift of the α-proton, as developed by Eliel[4], as the difference in chemical shift between the equatorial and axial α-protons was too small to make accurate calculation possible.

The second method of analysis which has been used and found to give reliable results,[5] is based on the band width (W) of the signal due to the α-proton. The method involves the use of Eq. 1 to calculate the equilibrium constant K, and hence ΔG was calculated from equation 2

$$K = \frac{W_e - W_a^e}{W_a^e - W_a} \tag{1}$$

$$\Delta G = -RT \ln K \tag{2}$$

Using firstly the results obtained from the 60 Mc/s spectrum of nitrocyclohexane, $K = 3{\cdot}7'$ and $\Delta G_{NO_2} = 0{\cdot}8$ kcal/mole, whilst at 100 Mc/s, $K = 7{\cdot}6$, and $\Delta G_{NO_2} = 1{\cdot}2$ kcal/mole. The results from the spectra of *cis*-4-methylnitrocyclohexane gave, at 60 Mc/s in $CDCl_3$, $K = 0{\cdot}50$, and a difference in free energy between the methyl and

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[4] E. L. Eliel, *Chem. & Ind.* 568 (1959).

[5] H. Feltkamp and N. C. Franklin, *Tetrahedron* **21**, 1541 (1965).

nitro groups (ΔG_{Diff}) of 0·4 kcal/mole. Using the generally accepted value $\Delta G_{\text{Me}} =$ 1·7 kcal/mole,[6] the ΔG value of the nitro group was 1·3 kcal/mole. At 100 Mc/s in $CDCl_3$, $K = 0{\cdot}52$, $\Delta G_{\text{Diff}} = 0{\cdot}4$ kcal/mole, and hence $\Delta G_{NO_2} = 1{\cdot}3$ kcal/mole.

A further method of analysis has recently been published,[7] and involves the calculation of the mole fraction (x) of the most stable conformer from Eqs. 3 and 4, and hence the calculation of K from Eq. 5.

$$J_{aa}{}^{ee} = x\, J_{aa} + (1 - x)\, J_{ee} \tag{3}$$

$$J_{ae}{}^{ea} = x\, J_{ae} + (1 - x)\, J_{ea} \tag{4}$$

$$K = \frac{x}{1 - x} \tag{5}$$

As the 60 Mc/s spectrum of nitrocyclohexane was not symmetrical, it was not possible to use the X approximation, i.e. the spectrum was of the A_2B_2R type, and not the A_2B_2X type. It was therefore not possible to measure the average coupling constants $J_{aa}{}^{ee}$ and $J_{ae}{}^{ea}$ directly from the splitting of the α-proton signal. At 100 Mc/s however the α-proton signal was symmetrical, and the X approximation could be applied; here it was found that $J_{aa}{}^{ee} = 10{\cdot}35$ c/s, and $J_{ae}{}^{ea} = 4{\cdot}20$ c/s. The values of J_{aa} and J_{ae} could be taken from the spectrum of *trans*-4-t-butylnitrocyclohexane, and the values of J_{ee} and J_{ea} from the spectrum of *cis*-4-t-butylnitrocyclohexane, both measured at 100 Mc/s. In view of the fact that $J_{ae}{}^{ea}$ lay within the range of the experimental error of J_{ae} and J_{ea}, Eq. 4 was not used, and so from Eq. 3 it was calculated that $x = 0{\cdot}87$, and hence $K = 6{\cdot}7$ giving $\Delta G_{NO_2} = 1{\cdot}1$ kcal/mole. It was not possible to use either the 60 Mc/s or 100 Mc/s spectra of *cis*-4-methylnitrocyclohexane in this method, as the coupling constants could not be determined directly from the splittings of the α-proton signals. On preliminary inspection both signals appeared to satisfy the X approximation i.e. geometrically regular and symmetrical about the centre, it was realized that these were examples of "deceptively simple spectra" and assumptions would have had to have been made, which were not justified in the circumstances.

An alternative approach to the question of suitable standards W_a and W_e to use in Eq. 1, or τ_e and τ_a to use in Eq. 6

$$K = \frac{\tau_e - \tau_a{}^e}{\tau_a{}^e - \tau_a} \tag{6}$$

is to determine the NMR spectra at low temperatures, so that the interchange rate $I_A \rightleftharpoons I_B$ is sufficiently slow to give separate signals due to the axial α-proton in conformer I_A and the equatorial α-proton in conformer I_B. The difficulties of this method have been discussed[8] and it was already known that nitrocyclohexane itself showed no splitting of the α-proton signal on cooling,[8] however the spectrum of *cis*-4-methylnitrocyclohexane at $-80°$ did show two peaks, but they were not completely separated. Because of solubility considerations the spectra were determined in CS_2 and at 25°

[6a] E. L. Eliel, E. W. Della and T. H. Williams, *Tetrahedron Letters*, 831 (1963); [b] M. Hanack, *Conformational Theory*, Academic Press, New York (1965); E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, Wiley, New York (1965).

[7] H. Booth, *Tetrahedron* **20**, 2211 (1964).

[8] W. C. Neikam and B. P. Dailey, *J. Chem. Phys.* **38**, 445 (1963).

the α-proton of *cis*-4-methylnitrocyclohexane appeared at 5·70 τ (band width 19·0 c/s); on cooling the main peak moved downfield to 5·63 τ (band width 13·0 c/s) and a second broad flat multiplet centered on 5·82 τ appeared. It was not possible to determine the band width of this peak, but there was no doubt that this was due to the axial α-proton on conformer II_A, whilst the position and band width of the peak at 5·63 τ confirmed that is was due to the equatorial α-proton in conformer II_B. It was not possible to use these low temperature measurements in the determination of the ΔG value of the nitro group for, as the two peaks were not completely separated, the areas under curves could not be determined and for the same reason neither could the band width or average coupling constant methods be used. An alternative method, that using the chemical shift and Eq. 6, could have been used, but because of the small separation of the two peaks, this would have been very inaccurate. It was of interest to compare these low temperature measurements with those made on the standard substances and for this reason the spectra of *cis*- and *trans*-4-t-butylnitrocyclohexane were also determined in CS_2; both the chemical shift and band widths were in good agreement with the low temperature measurements, and a subsidiary experiment showed that these chemical shifts were temperature independent, in these standard compounds.

DISCUSSION

It will have been noticed that the ΔG values for the NO_2 group obtained by the various methods show a considerable spread and the question arises, which of the results give the most accurate value? An equation of type 1 or 6 becomes very inaccurate, e.g. here when W_a^e approaches W_a or τ_a^e approaches τ_a, and for this reason it is not surprising that the difference of 1·8 c/s in band width of nitrocyclohexane results in the ΔG_{NO_2} varying from 0·8 kcal/mole to 1·2 kcal/mole when the spectra were measured at 60 Mc/s and 100 Mc/s respectively. The error in the measurement of the band width of *cis*-4-methylnitrocyclohexane however does not have such a large effect on the ΔG value of the nitro group (±1 c/s makes a difference of only 0·14 kcal/mole). It therefore appears that more weight can be placed on the values obtained from *cis*-4-methylnitrocyclohexane. During the revision of this paper, Trager and Huitric[9] reported that work on nitrocyclohexane, using partially deuterated *cis*- and *trans*-4-t-butylnitrocyclohexane as standards, and gave a value of $\Delta G_{NO_2} = 0{\cdot}78 \pm 0{\cdot}1$ kcal/mole. Although the value calculated in this paper is in agreement with this (for nitrocyclohexane at 60 Mc/s) both determinations suffer from the same mathematical errors previously mentioned. In view of the above comments, it would appear that results obtained from nitrocyclohexane should be given less weight and the value of 1·3 kcal/mole obtained from *cis*-4-methylnitrocyclohexane be taken as correct.

Interpretation of the spectra. Having completed the original assignment it was of interest to calculate the individual transitions in the α-proton part of the spectra. Both the 60 Mc/s and 100 Mc/s spectra of *cis*- and *trans*-4-t-butylnitrocyclohexane could be analysed using the X approximation, and so it was possible to measure directly the J_{AX} and J_{BX} coupling constants in the A_2B_2X system.

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[9] W. F. Trager and A. C. Huitric, *J. Org. Chem.* **30**, 3257 (1965).

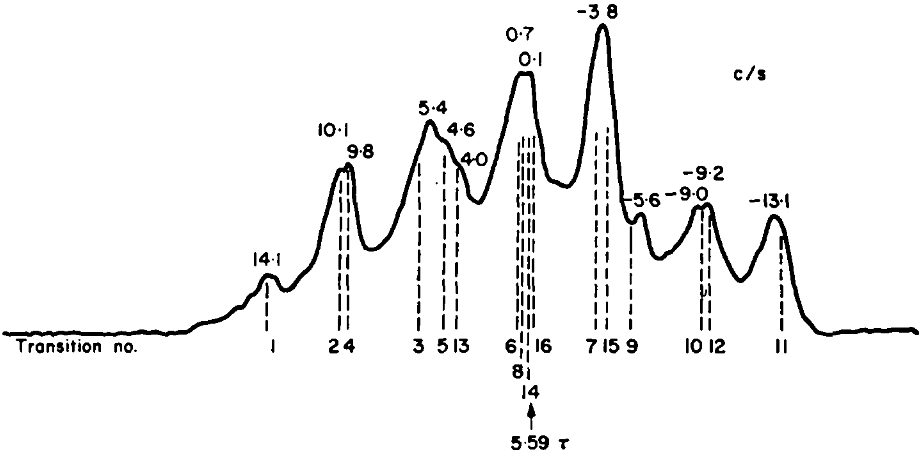

FIG. 2. The theoretical and experimental spectrum of the α-proton of nitrocyclohexane (at 60 Mc/s in $CDCl_3$).

The 60 Mc/s spectrum of nitrocyclohexane could not be treated by the X approximation as it showed a degree of unsymmetry about the centre. However as it bore a close resemblance to a "first order" multiplet, i.e. an A_2B_2R spectrum, being the intermediate case of the A_2B_2C and A_2B_2X systems, it was possible to solve this example by a second order perturbation method.[10]

The frequency of a transition of the R part is given by

$$\nu = \nu_R + (J_{AR}m_A + J_{BR}m_B) + \frac{1}{2}\frac{(J_{AR})^2}{\nu_R - \nu_A}[F_A(F_A + 1) - m_A(m_A + 1) + 2m_Am_R]$$

$$+ \frac{1}{2}\frac{(J_{BR})^2}{\nu_R - \nu_B}[F_B(F_B + 1) - m_B(m_B + 1) + 2m_Bm_R]$$

and the corresponding intensity (I) by

$$I = (F_R - m_R + 1)(F_R + m_R)\left[1 - 2\frac{J_{AR}m_A}{\nu_R - \nu_A} - 2\frac{J_{BR}m_B}{\nu_R - \nu_B}\right]$$

The coupling constants J_{AR} and J_{BR} were not the same as the coupling constants measured in the fixed t-butyl systems, but the time average values, J_{aa}^{ee} and J_{ae}^{ea} respectively. These time averaged values were calculated from Eqs. 4 and 5, using the x value of 0·79 taken from the 60 Mc/s spectrum of nitrocyclohexane. The values of ν_A and ν_B could not be obtained from nitrocyclohexane itself, but were taken from the best available model compound, 3-nitropentane, and the assumption was made that the axial and equatorial protons were moved to the same extent downfield and upfield respectively. It should be pointed out that any error in this assumption does not materially affect the calculation, the influence being less than 1%. The values which were taken in the calculation are set out in Table 2_A, and the full results of the calculation in Table 3. From Table 3 the theoretical transition lines were plotted and found to be in good agreement with the experimental spectrum (Fig. 2).

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[10] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance*, pp. 151–156, McGraw-Hill, New York (1959).

TABLE 2. VALUES OF THE CONSTANTS TAKEN IN THE CALCULATION OF THE THEORETICAL SPECTRA OF THE α-PROTON BY THE SECOND ORDER PERTURBATION METHOD

A. *Nitrocyclohexane*

$\nu_A = 115$ c/s, $\nu_B = 127$ c/s, $\nu_R = 265$ c/s, $J_{AR} = 9{\cdot}65$ c/s. $J_{BR} = 4{\cdot}06$ c/s.

$$A' = \frac{(J_{AR})^2}{\nu_R - \nu_A} = 0{\cdot}62 \text{ c/s} \qquad B' = \frac{(J_{BR})^2}{\nu_R - \nu_B} = 0{\cdot}12 \text{ c/s}$$

$$A'' = \frac{J_{AR}}{\nu_R - \nu_A} = 0{\cdot}064 \qquad B'' = \frac{J_{BR}}{\nu_R - \nu_B} = 0{\cdot}029$$

B. cis-4-*Methyl-nitrocyclohexane*

$\nu_A = 115$ c/s, $\nu_B = 140$ c/s, $\nu_R = 269$ c/s, $J_{AR} = 5{\cdot}50$ c/s, $J_{BR} = 4{\cdot}15$ c/s,

$$A' = \frac{(J_{AR})^2}{\nu_R - \nu_A} = 0{\cdot}196 \text{ c/s,} \qquad B' = \frac{(J_{BR})^2}{\nu_R - \nu_B} = 0{\cdot}133 \text{ c/s}$$

$$A'' = \frac{J_{AR}}{\nu_R - \nu_A} = 0{\cdot}035. \qquad B'' = \frac{J_{BR}}{\nu_R - \nu_B} = 0{\cdot}032.$$

Both the 60 Mc/s and 100 Mc/s spectra of *cis*-4-methylnitrocyclohexane (Fig. 3) were almost symmetrical quintets, but the splitting were not quite equal. Using Eqs. 3 and 4, it was possible to calculate the time averaged coupling constants J_{aa}^{ee} and J_{ae}^{ea} for this compound; these values were respectively 5·50 c/s and 4·15 c/s. Calculation of the theoretical spectrum by the second order peturbation method,[10] using the constants set out in Table 2_B was carried out, and although the overall fit was good, it was surprising that the pairs of lines 2, 4 and 5, 13 were not resolved, as their separation was over 1·3 c/s. As these doublets were not resolved, it would have been in order in this case to neglect the second order correcting terms, so that the above mentioned pairs of doublets would have given two singlets, with a separation of 1·35 c/s (c.f. Fig. 3).

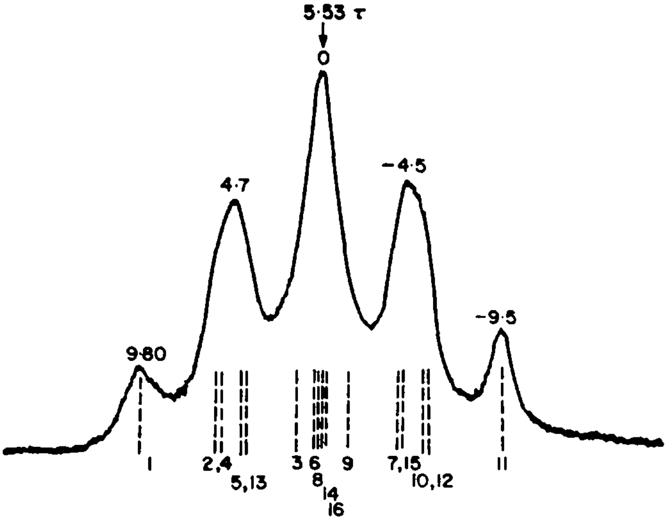

FIG. 3. The theoretical and experimental spectrum of the α-proton of *cis*-4-methylnitrocyclohexane (at 60 Mc/s in $CDCl_3$).

TABLE 3. TRANSITION ENERGIES AND INTENSITIES FOR A_2B_2R SYSTEM IN NITROCYCLOHEXANE (R TRANSITIONS, $m_R = -\frac{1}{2} \rightarrow m_R = +\frac{1}{2}$)

Line	F_Am_A	F_Bm_B	First order term	Numerical value in c/s	Second order term	Numerical value in c/s	Total numerical value	Intensity (relative)	Value
1	1, 1	1, 1	$J_{AR} + J_{BR}$	13·71	$\frac{1}{2}A' + \frac{1}{2}B'$	0·37	14·08	$1 - 2A'' - 2B''$	0·81
2	1, 1	1, 0	J_{AR}	9·65	$\frac{1}{2}A' + B'$	0·43	10·08	$1 - 2A''$	0·87
3	1, 1	1, −1	$J_{AR} - J_{BR}$	5·59	$\frac{1}{2}A' + \frac{1}{2}B'$	0·37	5·96	$1 - 2A'' + 2B''$	0·93
4	1, 1	0, 0	J_{AR}	9·65	$\frac{1}{2}A'$	0·31	9·96	$1 - 2A''$	0·87
5	1, 0	1, 1	$+ J_{BR}$	4·06	$A' + \frac{1}{2}B'$	0·68	4·74	$1 - 2B''$	0·94
6	1, 0	1, 0	0	0	$A' + B'$	0·74	0·74	1	1·00
7	1, 0	1, −1	$- J_{BR}$	−4·06	$A' + \frac{1}{2}B'$	0·68	−3·38	$1 + 2B''$	1·06
8	1, 0	0, 0	0	0	A'	0·62	0·62	1	1·00
9	1, −1	1, 1	$-J_{AR} + J_{BR}$	−5·59	$\frac{1}{2}A' + \frac{1}{2}B'$	0·37	−5·22	$1 + 2A'' - 2B''$	1·07
10	1, −1	1, 0	$-J_{AR}$	−9·65	$\frac{1}{2}A' + B'$	0·43	−9·22	$1 + 2A''$	1·13
11	1, −1	1, −1	$-J_{AR} - J_{BR}$	−13·71	$\frac{1}{2}A' + \frac{1}{2}B'$	0·37	−13·34	$1 + 2A'' + 2B''$	1·19
12	1, −1	0, 0	$-J_{AR}$	−9·65	$\frac{1}{2}A'$	0·31	−9·34	$1 + 2A''$	1·13
13	0, 0	1, 1	$+ J_{BR}$	4·06	$+ \frac{1}{2}B'$	0·06	4·12	$1 - 2B''$	0·94
14	0, 0	1, 0	0	0	$+ B'$	0·12	0·12	1	1·00
15	0, 0	1, −1	$- J_{BR}$	−4·06	$+ \frac{1}{2}B'$	0·06	−4·00	$1 + 2B''$	1·06
16	0, 0	0, 0	0	0	0	0	0	1	1·00

EXPERIMENTAL

cis-4-*Methylnitrocyclohexane.* Peracetic acid (3·7 g, 0·05 mole) [CARE] was dissolved in $CHCl_3$ (10 ml), and heated to boiling; the mantle was removed, and stereochemically pure *cis*-4-methylcyclohexylamine (1·13 g, 0·01 mole), dissolved in $CHCl_3$ (10 ml) was added dropwise over 30 min so that the reaction continued to boil vigorously. The resulting solution was then heated under reflux for 6 hr and poured into water (50 ml). The organic layer was separated and washed with NaOHaq (10%, 3 × 25 ml), 10% HCl (2 × 25 ml) and water (3 ×), before being dried over $MgSO_4$. The solvent was removed and the product chromatographed over Kieselgel, with a mixture of $CHCl_3$ (7 parts) and pet. ether (50–70°; 3 parts) as eluent. The product was finally distilled under vacuum to give a colourless oil. (Found: N, 9·7. Calc. for $C_7H_{13}NO_2$: N, 9·75%.) The NMR spectra were determined using Varian A60 and Varian HA 100 machines, approximately 10% solutions were used throughout, and the band width measurements are accurate to ±0·3 c/s.

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