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N.M.R. EVIDENCE FOR THE TWIST CONFORMATIONS OF SOME *cis*-1,4-DISUBSTITUTED CYCLOHEXANES

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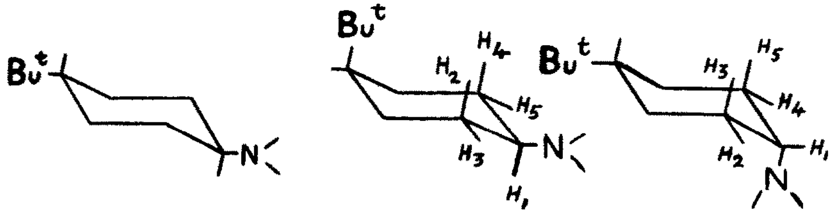
The use of the phthalimido group in enforcing the conformational homogeneity of substituted cyclohexanes has been reported (1). The n.m.r. spectra of the phthaloyl derivatives of *cis*- and *trans*-2-alkylcyclohexylamines have features which indicate immediately the stereochemistry of the molecules (1,2). In an effort to assess more accurately the size of the phthalimido group, we have examined the n.m.r. spectra of *cis*- and *trans*-4-*t*-butyl-1-phthalimidocyclohexane.

The *trans*-imide gave the spectrum expected for a molecule fixed in the chair conformation I. The ring proton α- to the nitrogen atom (hereafter referred to as 'the α-proton') appeared at τ = 5.78 as a triplet (J_{aa} = 11.1 c./sec.), each component being a triplet (J_{ae} = 3.5 c./sec.). The α-proton signal in the spectrum of the *cis*-isomer appeared at τ = 5.56 as an almost symmetrical 1,4,6,4,1-quintet, the spacings between the somewhat unsharp lines being about 5.6 c./sec. It is probable, therefore, that the coupling between the α-proton and each of the four protons on adjacent carbon atoms is about 5.6 c./sec.



I II III

This signal is incompatible with any of the following possibilities for the conformation of the molecule:

(i) chair II, as this should give an α-proton resonance similar to that of the <u>trans</u>-isomer I;

(ii) chair III, as the α-proton signal of this conformation is expected to be a narrow signal, probably unresolved, of which the one-fifth-band width ($\sim 2J_{ae} + 2J_{ee}$) is only about 11-15 c./sec;

(iii) mixture of rapidly interconverting chairs II and III, since in this case the only situation producing <u>four equal</u> couplings occurs when the coupling is about 3-4 c./sec. To appreciate this, consider the averaged couplings of H_1 with H_2 H_3 etc. in a mixture of II and III containing fraction x of II.

$$\text{Average } J_{12} = \text{Average } J_{14} = x\,J_{aa} + (1-x)\,J_{ee}$$

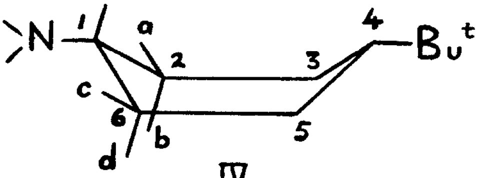
$$\text{Average } J_{13} = \text{Average } J_{15} = x\,J_{ae} + (1-x)\,J_{ae}$$

$$= J_{ae} = 3\text{-}4 \text{ c./sec.}$$

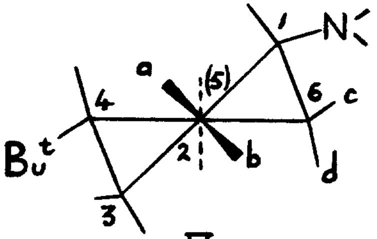
If, therefore, Average J_{12} = Average J_{13}, the common value must be about 3-4 c./sec. This is confirmed from calculated spectra for the α-proton of the system II $\rightleftarrows$ III, for varying values of x, and using J_{aa} = 11.5 c./sec., J_{ae} = 3.6 c./sec. and J_{ee} 1.5 to 3 c./sec. (for explanation of choice of values, see later). The above method of averaging coupling constants is considered in greater detail in a forthcoming paper (3).

The most likely explanation for the observed α-proton signal is that the molecule eliminates some of the strain involved in the chair conformation III (bulky group axial) by spending most of its time in twist conformations, of comparable energy, which are undergoing interconversion. Now the twist conformation (4,5) has two kinds of carbon atom; two of the atoms (C_2 and C_5 in V) are like those of cyclopentane, with respect to the environment of the attached bonds, whilst four of the atoms (C_1 C_3 C_4 and C_6 in V) are in the same respect similar to those of cyclohexane. In the general case, six twist conformations have to be visualised when considering the variation in dihedral angle between specific C-H bonds attached to adjacent carbon atoms. However, in the case of cis-4-t-butyl-1-phthalimidocyclohexane, the two twist conformations which involve 'bowsprit-flagpole' interaction between the bulky groups may be neglected.

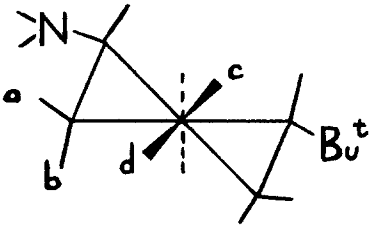
The situation is best understood from Dreiding models, by starting with the true boat IV and slowly rotating, clockwise or anticlockwise, carbon atoms 1 2 and 6 about a line joining C_1 to C_4. This rotation does not involve a close approach of the t-butyl and phthalimido groups, provided it stops short of the two unstable conformations mentioned. For clockwise rotation, conformation V is soon reached, in which the dihedral angles between the α-proton and protons a b c and d are 33°, 153°, 71° and 169° respectively. Further clockwise movement causes the molecule to pass through a boat form into the twist conformation VI, in which the dihedral angles for a b c and d are now 33°, 87°, 33° and 153° respectively. Anticlockwise rotation from IV gives the twist conformations VII and VIII. The situation is summarized in the TABLE.



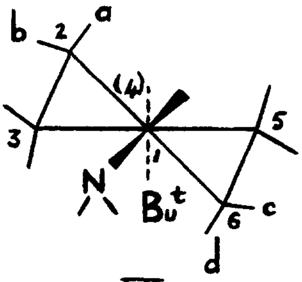
IV



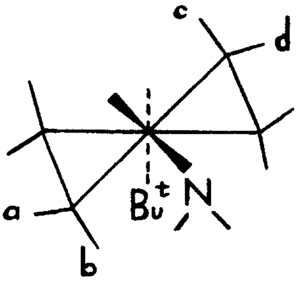
V



VII



VI



VIII

TABLE

Twist Conformation	Dihedral angles between α-proton and protons at C_2 and C_6			
	a	b	c	d
V	33	153	71	169
VI	33	87	33	153
VII	71	169	33	153
VIII	33	153	33	87

The measured coupling constants J_{aa} and J_{ae} for the α-proton of phthaloyl cyclohexylamines are in the ranges 10.0-12.3 and 3.0-4.1 c./sec. respectively (1,2). The average values (14 examples) are 11.5 and 3.6 c./sec. respectively (6,7). No values of J_{ee} are available for the system under discussion, but a rough assessment can be made from the α-proton signal in the n.m.r. spectrum of N-(cis-4-t-butylcyclohexyl) succinamic acid. This signal, due to an equatorial proton coupled to two equatorial and two axial protons, is not resolved. However, the following relationships will hold, approximately:

(a) $\frac{2}{3}$-band width $= 2(\frac{J_{ae} + J_{ee}}{2}) = J_{ae} + J_{ee}$

(b) $\frac{1}{5}$-band width $= 2\ J_{ae} + 2\ J_{ee}$

The observed spectrum gave the following values: $\frac{2}{3}$-band width = 5.6 ± 0.5 c./sec.; $\frac{1}{5}$-band width = 11.5 ± 1.0 c./sec. From the average, and using J_{ae} as 3.6 c./sec., the following values are obtained: J_{ee} = 2.08 ± 0.5 c./sec., and Average $J_{ae/ee}$ (=average of J_{ae} and J_{ee}) = 2.84 ± 0.25 c./sec.

The values of 11.5 c./sec. and 2.84 c./sec. for J_{aa} and Average $J_{ae/ee}$, respectively, suggest that the Karplus equation for the $-CH_2-CH[N(COR)_2]-$ fragment of acylated cyclohexylamines is of the form

$$J = 11.4 \pm 1 \cos^2 \phi$$

where ϕ is the dihedral angle involved. Now the angles 33°, 71°, 87°, 153° and 169° yield J values of 8.0 ± 0.7, 1.25 ± 0.1, 0, 9.1 ± 0.8, and 11.0 ± 1 c./sec. respectively. Assuming the twist conformations V to VIII to be of comparable energy, an assumption which appears justified on inspection of models, the averaged coupling constants for interaction of the α-proton with protons a b c and d are approximately 6.3 ± 0.6, 7.3 ± 0.7, 6.3 ± 0.6 and 7.3 ± 0.7 c./sec. respectively. Thus an almost symmetrical quintet, with splittings of 5.7 to 8 c./sec., is predicted for the α-proton signal of *cis*-4-*t*-butyl-1-phthalimidocyclohexane, if the molecule spends *all* its time in rapidly interconverting twist conformations. As the observed splittings are about 5.6 c./sec., it is likely that there is some contribution also from the chair conformation (III).

Mobile twist conformations are also important in the case of *cis*-4-*t*-butyl-1-succinimidocyclohexane. In the n.m.r. spectrum, the α-proton at τ = 5.80 is a 1,4,6,4,1-quintet with separations of about 5.8 c./sec. *cis*-4-*t*-Butylcyclohexyltrimethylammonium iodide is another molecule which is expected to avoid the chair conformation. Unfortunately, the α-proton signal, at τ = 6.0 in the n.m.r. spectrum, was not resolved, but its broadness (½-band width ~ 18 c./sec.) eliminates the possibility of a major contribution from a chair in which $\overset{+}{N}Me_3$ is axial. Garbisch and Patterson (8) have suggested that *cis*-4-*t*-butyl-1-phenylcyclohexane exists to an appreciable extent in a boat form. It is noteworthy that, in the n.m.r. spectrum of this hydrocarbon at 150°, the benzylic proton appears as a quintet, with spacings of 4.7 c./sec.

It is probable that cyclohexanes substituted in the 1,3-positions, and in a *trans*-manner, by space-demanding groups will also assume mobile twist conformations (9). In the case of *cis*-1,2-disubstituted cyclohexanes, mobile twist conformations are unlikely since the flexibility involves movement through boat forms with the bulky groups in eclipsed positions.

Spectra were measured in chloroform (amides), benzene (amides) and NaOD (acids), using an A.E.I. R.S.II spectrometer. We are indebted to Dr. H. Feltkamp, University of Tübingen, for a sample of pure *cis*-4-*t*-butylcyclohexylamine, and to Dr. N. C. Franklin for help with the experimental work.

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