Conformational Analysis of Cyclohexane Derivatives. The *A* Value of a Benzyl Group

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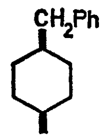
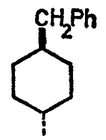
At −97·6° the chair–chair equilibrium constant in *cis*-1-benzyl-4-methylcyclohexane is 1·35, the conformation with an equatorial benzyl group being more stable by 0·11 kcal mol^{-1}. The *A* value of the benzyl group is 1·81 kcal mol^{-1}.

THE preferences of a large number of substituents for the equatorial as opposed to the axial position in cyclohexane has now been determined [1-3] and their expression in terms of a free energy difference (the *A* value) [4] has become a convenient measure of the size of such a substituent. *A* Values reflect the interactions in the two positions in cyclohexane, but are also a useful basis for the discussion of interactions in other situations.

The *A* value of a benzyl group has not been reported, but it is of some interest in view of the many instances of its use as a probe in n.m.r. studies of conformations.[5] This use is based on the fact that in an asymmetric environment the methylene hydrogens are expected to appear as an AB quartet, while they appear as a singlet in the absence of asymmetry. Since the probe may itself affect the system under study, some estimate of its size seems desirable. Direct examination of benzylcyclohexane itself is not a promising technique since on the basis of an expected *A* value of 1·8 kcal mol^{-1}, there is only 4·6% of the axial isomer present at 25°, and 0·53% present at −100°, and there is no obvious physical method of distinguishing these conformations and measuring their relative abundance accurately. I chose to compare the size of a benzyl group with that of a methyl group from the conformational equilibrium in *cis*-1-benzyl-4-methylcyclohexane (1) as shown by separate signals for the two conformations in the n.m.r. spectrum at low temperature.



(1)



(2)

RESULTS

The striking feature of the room-temperature n.m.r. spectrum of *cis*-1-benzyl-4-methylcyclohexane (1), is a doublet (*J* 7·2 Hz) at δ 2·58 due to the benzyl methylene hydrogens (Figure a). The splitting of the signal is due to coupling with the adjacent methine hydrogen. At −97·6°, the signal appears as two doublets at δ 2·65 and 2·45 (*J* 7·8 and 4·5 Hz respectively; Figure b).

The two low-temperature doublets are of slightly different intensities, the ratio of the areas under the peaks being 1·35 (±0·14) : 1, the downfield doublet being more intense. This corresponds to 57·4 ± 2·7% of the more stable isomer

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[1] For a review see J. A. Hirsch, *Topics Stereochem.*, 1967, **1**, 199.

[2] F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.*, 1971, **3**, 139.

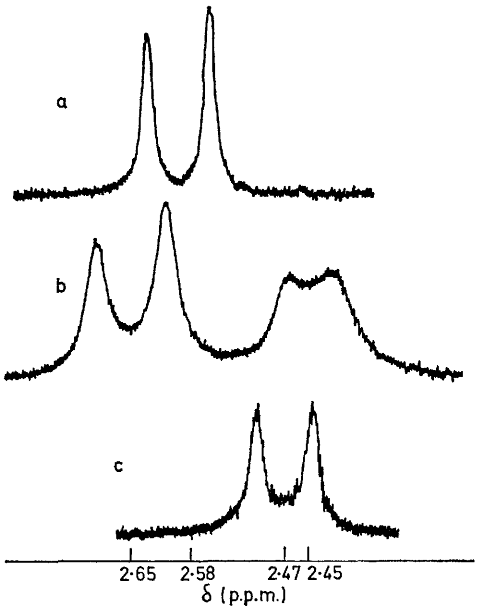
[3] F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, 1969, **91**, 344.

[4] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.

[5] I. O. Sutherland, *Ann. Reports N.M.R. Spectroscopy*, 1971, **4**, 71, lists many examples, those from studies of nitrogen inversion being particularly numerous.

at equilibrium, and a standard free energy difference between isomers of 105 ± 39 cal mol^{-1} at −97°.

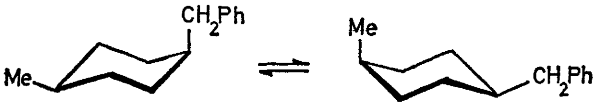
In contrast, the spectrum of the *trans*-isomer (2) is essentially the same over a wide range of temperatures, the methylene signal appearing as a doublet at δ 2·47 (*J* 6·6 Hz; Figure c).



100 MHz N.m.r. spectra of the benzylic methylene groups of (1) and (2): a, (1) at ambient temperature; b, (1) at −97·6°; c, (2) at ambient temperature. Small traces of (2) can be seen in spectrum a . δ Values indicated are for midpoints of doublets

DISCUSSION

N.m.r. Spectrum and Structure.—Compound (1) is expected to exist as an equilibrium mixture of conformations (3) and (4), whereas (2) should exist solely as (5). While the interconversion of (3) and (4) is expected to be rapid on the n.m.r. timescale at room temperature it should be slow at −100°, and separate signals for (3) and (4) should be present in the n.m.r. spectrum.[6] Any group in (1) should thus give two sets of signals in the low temperature n.m.r. spectrum, and this explains the appearance of two doublets for the benzyl methylene group at −97·6°.



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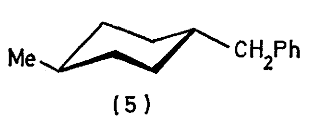
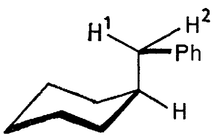


(5)

The assignment of the two doublets to equatorial and axial benzyl groups is not straightforward. The signal of the *trans*-isomer in which the benzyl group is expected to be 100% equatorial is upfield of the signal of the *cis*-isomer at room temperature. Since the benzyl group in the *cis*-isomer is expected to be part axial–part equatorial, it might be concluded that the axial signal should be downfield from the equatorial signal in the low temperature spectrum of the *cis*-isomer. This would be a valid conclusion only if the benzyl methylene signal shift is independent of the disposition equatorial or axial, of the 4-methyl group.

In fact the *upfield* of the two benzyl signals in the *cis*-isomer is assigned to the axial benzyl group on the basis of the much greater width of these signals. An axial group should have much broader signals due to small long-range coupling with axial hydrogens on the two adjacent carbon atoms.[7] An attempt to confirm the effect of long range coupling on the axial signal by decoupling was vitiated by the apparent coincidence of the signals of these axial hydrogens and the methine proton causing the large splitting of the benzyl signal.



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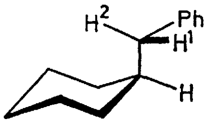

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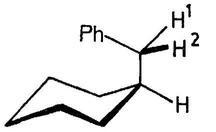

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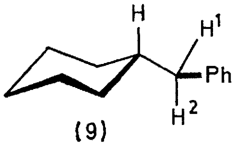

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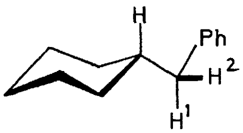

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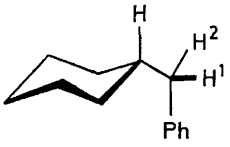

(11)

The coupling of the benzyl group with the adjacent methine proton varies in an interesting way. In (5) the equatorial benzyl group has a coupling constant of 6·6 Hz independent of the temperature while in (4) the equatorial benzyl group has a coupling constant of 7·2 Hz. Thus the disposition of the methyl group in the 4-position affects not only the chemical shift but also the coupling at the benzyl group and it would seem reasonable to attribute this to varying distortions which change dihedral angles at the opposite end of the molecule.

It is reasonable to imagine that the conformation about the benzyl–ring bond is an equal mixture of (9) and (10) with little contribution from the form (11) with the phenyl group gauche to two carbon–carbon bonds. The observed coupling constant is then the mean of those

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[6] For a discussion of the inversion of conformation of six-membered rings see J. E. Anderson, *Fortschr. Chem. Forsch.*, in the press.

[7] K. L. Williamson, T. Howell, and T. A. Spencer, *J. Amer. Chem. Soc.*, 1966, **88**, 325.

arising from a *ca.* 180 and a *ca.* 60 dihedral angle. Considering conformation (3) it would be expected that the forms (6) and (7) should predominate, so that coupling constants should again correspond to dihedral angles of *ca.* 180 and 60°. The observed splitting for (3) should then be close to that for (4) and (5). In fact the coupling constant in (3) is considerably smaller, the effect being much larger than the difference between (4) and (5) (coupling constants are 4·5, 6·6, and 7·8 Hz respectively). From this it would seem that there are *large* distortions in (3) compared with (4) and (5) or perhaps that conformation (8) (in which dihedral angles are both 60° and coupling constants should be smaller) is populated to some extent.

Conformational Equilibria.—The *A* value of a methyl group has been determined by several methods,[1] and the most likely value for this [8-10] is *ca.* 1·7 kcal mol^{-1}. *A* Values for other substituents can be found by studying equilibria in *cis*-4-substituted 1-methylcyclohexanes in the manner done in this work and adjusting the free energy difference found by 1·7 kcal mol^{-1}.

This approach implies that the *A* value for a substituent is unaffected by the methyl group in the 4-position, but the validity of this assumption has been questioned [3,11] and is cast further in doubt by the distortions suggested by the difference in coupling constant between (4) and (5) remarked above. Direct evidence of the effect of substituents in the 4-position on the conformational analysis of the 1-position in cyclohexane has been reported. Lambert and his co-workers [12] found that substitution of *both* hydrogens in the 4-position by methyl groups reduced *A* values for halogen atoms by *ca.* 60 cal mol^{-1} on average. Eliel and his co-workers [13] have found that in the 4-alkylcyclohexanols, *A* values are additive, and thus a single substituent has no effect on the conformation at the other end of the molecule. The noticeable effect of two 4-substituents has been confirmed by Vandenbroucke and Anteunis,[14] who found that equilibria in 4-alkyl-4-methylcyclohexanone dimethyl acetals could not be accurately predicted on the basis of known *A* values.

Since the methyl *A* value of 1·7 refers to room temperature, it would be of interest to know the position of the conformational equilibrium in (1) at this temperature as well. This might be decided, in theory, from the coupling constant of the benzyl group at this temperature which should be a weighted average of the two very different constants observed for (3) and (4) at low temperatures. For (1), the coupling constant of the benzylic group at ambient probe temperature is 7·2 Hz while those for (3) and (4) at −96·5° are 4·5 and 7·8 Hz respectively. If it is assumed that the coupling constant in each conformer of the *cis*-isomer is independent of temperature, then the ambient temperature coupling constant suggests that there is 82% of the equatorial isomer present. From this, and the directly measured results at −97·6° the *cis*-conformation with the benzyl group axial is of lower enthalpy by more than 1 kcal mol^{-1}, the entropy difference is −6·6 cal mol^{-1} K^{-1}, and the *A* value of the benzyl group is *ca.* 0·7 kcal mol^{-1} at ambinet temperature.

These values seem so unreasonable that the original premise is likely to be wrong, that is, the coupling constant in each conformation of the *cis*-isomer is not temperature independent. That these should vary is reasonable since the value in each of the conformers (3) and (4) is itself a further temperature-dependent average of rotational conformers (6)—(8), and (9)—(11) respectively.

This leads to the rather unsatisfactory conclusion that the *A* value for the benzyl group is 1·81 kcal mol^{-1} at −97·6°, but that its value at room temperature cannot be derived from this. Careful measurements of equilibria of this type, *e.g.*, work by Celotti *et al.*,[15] have indicated that entropy differences between conformers are not zero, that is, the *A* values are temperature dependent. If, as suggested by Allinger and his co-workers, on the basis of calculations,[16] there should be a small negative entropy difference between the axial and equatorial conformation of a group like a benzyl group, the *A* value for this group at ambient temperature should be somewhat larger than 1·81 kcal mol^{-1}.

This *A* value is very similar to that determined for an ethyl group and other CH_2Y [1] groups. The benzyl group thus has spatial requirements slightly greater than a methyl group. Two further conclusions stand out however; first compound (1) is distorted compared with benzylcyclohexane to an extent which cannot be quantified, and secondly the conformation about the benzyl–cyclohexane bond is quite temperature dependent.

EXPERIMENTAL

N.m.r. spectra were recorded using a Varian HA100 spectrometer of 100 MHz operating frequency. Chemical shifts were calibrated using a Varian V 4315 counter. Coupling constants are based on a first-order analysis of line separations in doublets. Areas under peaks were measured using a planimeter and were corrected for small traces of compound (2) present in the sample of (1), and for the irregularity of the horizontal scale. As for this second point, it was found that operating at 100 Hz sweepwidth, 1 mm at the left-hand end of the chart represented about 0·191 Hz whereas 1 mm at the right-hand end of the chart represented about 0·201 Hz. The area under the upfield peak is thus less than if it were recorded at the same point on the chart as the downfield peak.

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[8] C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488.

[9] N. L. Allinger and S.-E. Hu, *J. Org. Chem.*, 1962, **27**, 3417.

[10] E. W. Garbisch, results quoted in F. A. L. Anet, C. H. Bradley, and G. W. Buchanan, *J. Amer. Chem. Soc.*, 1971, **93**, 258.

[11] An early discussion with references is given by E. L. Eliel, *J. Chem. Educ.*, 1960, **37**, 126.

[12] D. S. Bailey, J. A. Walder, and J. B. Lambert, *J. Amer. Chem. Soc.*, 1972, **94**, 177.

[13] E. L. Eliel, S. M. Schroeter, T. J. Brett, F. J. Biros, and J.-C. Richer, *J. Amer. Chem. Soc.*, 1966, **88**, 3327.

[14] W. Vandenbroucke and M. Anteunis, *J.C.S. Perkin II*, 1972, 123.

[15] J. C. Celotti, J. Reisse, and G. Chiurdoglu, *Tetrahedron*, 1966, **22**, 2249.

[16] N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. van Catledge, *J. Amer. Chem. Soc.*, 1968, **90**, 1199.

Samples were *ca.* 0·3M in dichlorodifluoromethane as solvent and contained small amounts of methylene chloride and tetramethylsilane as reference compounds. Temperatures were measured as described previously.[17] Error limits were estimated from the mean difference between measured values and the average value, and this difference was then doubled to allow for any other systematic errors, the result being the ± figures quoted in the Results section.

1-*Benzyl*-4-*methylcyclohexanol*.— 4-Methylcyclohexanone (0·8 mol) was added to benzylmagnesium chloride (1·0 mol) in diethyl ether. After refluxing for 3 h the resultant complex was hydrolysed with dilute hydrochloric acid to give a 97% yield of the product, presumably a mixture of isomers, a viscous liquid, b.p. 96° at 0·03 mmHg.

4-(*Methylcyclohex*-1-*enyl*)*phenylmethane*.—This was prepared by the method of Brewster and Privett [18] and from its n.m.r. spectrum contaminated with 15% of the exocyclic double bond isomer.

1-*Benzyl*-4-*methylcyclohexanes* (1) *and* (2).—The mixture obtained from the preparation of (4-methycyclohex-1-enyl)-phenylmethane was hydrogenated in ethyl acetate solution using 10% palladium on charcoal. The product, b.p. 55—56° at 0·04 mmHg, appeared to be 53% *trans*-isomer (2) and 47% *cis*-isomer (1) (g.l.c., 100 ft capillary column coated with dinitrophenyl naphthyl ether at 100° and 2·5 lb in^{-2}) (Found for the mixture: C, 89·15; H, 10·5. Calc. for $C_{14}H_{20}$: C, 89·3; H, 10·7%). Preparative g.l.c. (20 ft × $\frac{3}{4}$ in Carbowax 20M column at 148°) gave first the *trans*-isomer, n_D^{25} 1·5076, then the *cis*-isomer, n_D^{25} 1·5165. Preparation of an unspecified mixture of isomers, n_D^{20} 1·5151, b.p. 266·5—267·5°, has been reported previously.[19]

I am grateful to Mr. C. J. Cooksey for the preparation of (1) and (2).

[3/1564 *Received, 25th July,* 1973]

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[17] J. E. Anderson and H. Pearson, *Chem. Comm.*, 1971, 871.

[18] J. H. Brewster and J. E. Privett, *J. Amer. Chem. Soc.*, 1966, **88**, 1419.

[19] A. N. Niyazov and K. N. Siderenko, *Izvest. Akad. Nauk Turkmenistan S.S.R., Ser. fiz.-tekhn., Khim. i Geol. Nauk*, 1962, 49 (*Chem. Abs.*, 1963, **59**, 2693c).