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THE AVERAGE COUPLING CONSTANTS OF PROTONS ON ADJACENT CARBON ATOMS IN MOBILE CYCLOHEXANE SYSTEMS

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Abstract—A method is described and discussed in which signals in the NMR spectra of mobile cyclohexane systems are analysed by using averaged coupling constants. The method accounts satisfactorily for some published spectra and allows rough values of ΔG (equatorial → axial) to be calculated for the substituents NH_2, OH and Br.

IN FIXED cyclohexane systems, the magnitude of the coupling constants J_{HH} between protons on adjacent atoms depends on the dihedral angle involved and on the nature of the substituents attached to the carbon atoms. A recent survey[1] of such coupling constants included values for many types of six-membered ring compounds. For cyclohexanes, the reported values of J_{aa} range from 10 to 12·5 c/s and of J_{ae} they range from 3·5 to 4·5 c/s. The only accurate value of J_{ee} is 2·72 c/s.[2]

The following treatment of mobile cyclohexane systems is based on that used by Pople *et al.*[3] for substituted ethanes. Two basic assumptions are made: (i) interconversion is sufficiently rapid for the chemical shifts and coupling constants to be averaged; (ii) the time of transition between conformations is short compared with the residence times.

The general case of a monosubstituted cyclohexane $C_6H_{11}X$ will be considered. The molecule is assumed to be undergoing rapid ring-inversion between conformation (I), in which X is equatorial, and conformation (II), in which X is axial. We will consider the ring proton on the carbon atom which also holds the substituent X; this proton will hereafter be referred to as 'the α-proton.' There is normally an appreciable difference, 0·3 to 0·8 ppm, in chemical shift between equatorial and axial protons which are in structurally identical environments. The resonance signal of the equatorial proton is generally at lower field than that of the axial proton. However, at room temperature, the rate of ring inversion appears to be much greater than the frequency difference between the signals for e and a protons, and thus a single resonance, representing an averaged chemical shift, is observed. As far as the author is aware, no cyclohexane has so far been examined for which the NMR spectrum at room temperature shows signals attributable to *both* possible chair conformations. Most common substituents are more electronegative than —CH_2— and exert such a marked deshielding effect on the α-proton that the signal for this proton is clearly seen at a field much

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[1] A. C. Huitric, J. B. Carr, W. F. Trager and B. J. Nist, *Tetrahedron* **19**, 2145 (1963).

[2] F. A. L. Anet, *J. Amer. Chem. Soc.* **84**, 1053 (1962).

[3] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* p. 380. McGraw-Hill, New York (1959).

lower than that for the remaining ring protons. A first-order analysis of the α-proton signal is often possible, because the coupling constants involved are small compared with the difference in chemical shift between the α-proton and the protons on adjacent carbon atoms.

I
x

II
1-x

If we wish to predict the appearance of the α-proton signal of the monosubstituted cyclohexane $C_6H_{11}X$, it is necessary to determine the averaged coupling constants between H_1 and each of the protons H_2 H_3 H_4 and H_5. Let the mixture of I and II contain fraction x of I. Then

Average coupling constant between H_1 and H_2

$$= \text{Average } J_{12} = xJ_{ae} + (1 - x)J_{ea}$$

$$\hat{=}\ J_{ae}$$

$$\text{Similarly, Average } J_{14} = J_{ae}$$

$$\text{Average } J_{13} = xJ_{aa} + (1 - x)J_{ee} = J^*$$

$$\text{Average } J_{15} = xJ_{aa} + (1 - x)J_{ee} = J^*$$

Assuming first order conditions (i.e. $\delta_{12} \gg J_{12}$ etc.), the resulting signal for the α-proton H_1 is a 1,2,1-triplet, with separations equal to J^*, each component of the triplet being itself a triplet, with separations equal to J_{ae}.

The validity of the treatment is easily established, from spectra in the literature, for the extreme case of $x = 1$, when the signal should be a triplet (separations J_{aa}), each component itself a triplet (separations J_{ae}). For example, the conformationally homogeneous *trans*-4-t-butyl-1-nitrocyclohexane[4] and *trans*-4-t-butyl-1-phthalimidocyclohexane[5] give α-proton signals which show fine structure in agreement with expectations. For the extreme case of $x = 0$, the signal should be a triplet (separations J_{ae}), each component a triplet (separations J_{ee}). Since the splittings are small and comparable, the observed signal may not show fine structure, and may appear as a fairly smooth envelope. Such a signal has been recorded, for example, for *cis*-4-t-butyl-1-nitrocyclohexane[4] and is also shown by *cis*-4-t-butylcyclohexylamine. These signals may be analysed using widths at carefully chosen fractional heights (see later). The method is only useful if the recorded spectrum has a steady base line, and this in turn is not possible if the sample is in short supply, or is relatively insoluble in normal solvents, or if the spectrometer is not giving peak performance.

For values of x between 0 and 1, the appearance of the α-proton signal will depend critically on the values of J_{aa} J_{ae} and J_{ee}, and on the value of x. The signal will rarely be completely resolved, because of the closeness of some of the lines. However, calculations demonstrate that some combinations of coupling constants give an α-proton signal which is a symmetrical quintet or septet, due to the fortuitous

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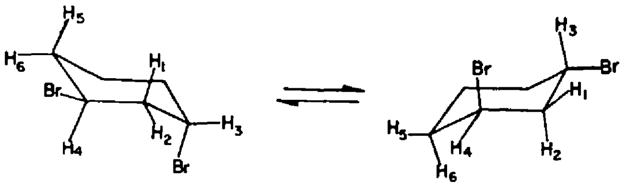
[4] A. C. Huitric and W. F. Trager, *J. Org. Chem.* **27**, 1926 (1962).

[5] H. Booth and G. C. Gidley, *Tetrahedron Letters* (in the press).

superposition of lines. In any case, measurements of line separations, or of the band width, combined with a knowledge of J_{aa} J_{ae} and J_{ee} for the system under examination, allows rough values of x to be determined. Finally, it is essential to consider various values of x in the vicinity of the rough value obtained, calculate the appearance of the α-proton signal in each case, and make comparison with the observed signal. From x, the conformational free energy change in moving an equatorial substituent into an axial position (ΔG or A-value) can be calculated.

The treatment requires values of J_{aa} J_{ae} and J_{ee} for each system examined. J_{aa} and J_{ae} can usually be obtained by direct measurement of the resolved α-proton peak in a conformationally homogeneous system containing the substituent equatorial ($x = 1$, see above). Accurate evaluation of J_{ee} is difficult, but an approximate figure can be obtained from the band width of the α-proton signal for the homogeneous system containing the substituent axial ($x = 0$, cf.[5]).

First, the general validity of the method of averaging will be tested by reference to a mobile system in which the position of equilibrium is self-evident. *trans*-1,3-Dibromocyclohexane exists as a mixture of interconverting conformations III and IV.



III IV

In each conformation, one bromine is axial and one equatorial. Therefore the conformations are energetically equivalent and should be present in the mixture in equal proportions. We will use the figures which Lemieux and Lown[6] deduced from dipole moment data and NMR studies, i.e. $J_{aa} = 10{\cdot}2$, J_{ae} (mean) $= 3{\cdot}7$ and $J_{ee} = 2{\cdot}0$ c/s for the fragment $—CH_2—CH(Br)—$ which is part of a cyclohexane ring. Consider first the methylene protons at C_2, the resonance for which appears as a triplet, with separations of 5·5 c/s.[7,8] These protons, H_1 and H_2, form the A_2 part of an A_2X_2 system, since rapid interconversion of the two equivalent conformations will give H_1 and H_2 the same chemical shift, and also H_3 and H_4, the same chemical shift. Now

$$\text{average } J_{14} = \tfrac{1}{2}(J_{aa} + J_{ee}) = J$$
$$\text{average } J_{23} = \tfrac{1}{2}(J_{ee} + J_{aa}) = J$$
$$\text{average } J_{13} = \tfrac{1}{2}(J_{ae} + J_{ea}) \simeq J_{ae} = J'$$
$$\text{average } J_{24} = \tfrac{1}{2}(J_{ea} + J_{ae}) \simeq J_{ae} = J'$$

Using the above figures,

$$J = 6{\cdot}1 \text{ c/s}$$
$$J' = 3{\cdot}7 \text{ c/s}$$

Also, using the nomenclature of Abraham and Bernstein,[9]

$$J_{12} = J_A = 10 - 20 \text{ c/s} \quad \text{and} \quad J_{34} = J_X \simeq 0$$

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[6] R. U. Lemieux and J. W. Lown, *Canad. J. Chem.* **42**, 893 (1964).

[7] B. Franzus and B. E. Hudson, Jr., *J. Org. Chem.* **28**, 2238 (1963).

[8] H. M. van Dort and T. J. Sekuur, *Tetrahedron Letters* 1301 (1963).

[9] R. J. Abraham and H. J. Bernstein, *Canad. J. Chem.* **39**, 216 (1961).

Then $(J - J')^2/2(J_A - J_X)$ lies between 0·144 and 0·288 c/s, which is less than the line width of most spectrometers. Consequently, the fact that the methylene protons at C_2 appear as a simple triplet is intelligible (cf.[9]). Now the separation of the lines in such a triplet is *not* $\frac{1}{2}(J_{aa} + J_{ee})$, as suggested by a number of authors,[7,8,10] but is $\frac{1}{2}(J + J')$. In this case $\frac{1}{2}(J + J')$ is 4·9 c/s, in reasonable agreement with the observed separation of 5·5 c/s. The triplet, separation 5·6 c/s, due to the C_2 protons in *trans* cyclohexane-1,3-diol[10] may be explained in a similar way.

Next, consider the ring protons H_3 and H_4 in *trans*-1,3-dibromocyclohexane; these are equivalent in terms of both chemical shift and coupling constants, so that one need only consider one of them.

$$\begin{aligned} \text{Average } J_{41} = \text{average } J_{45} &= \tfrac{1}{2}(J_{aa} + J_{ee}) \\ &= 6{\cdot}1 \text{ c/s} \\ \text{Average } J_{42} = \text{average } J_{46} &= \tfrac{1}{2}(J_{ae} + J_{ea}) \\ &= 3{\cdot}7 \text{ c/s} \end{aligned}$$

Thus, of the four couplings suffered by H_4, two will be 6·1 c/s and two will be 3·7 c/s. The observed signal for H_4 may not be fully resolved, but a calculated spectrum shows that the following relationship will hold, approximately:

$$\begin{aligned} \tfrac{1}{4}\text{-band width} &= 2(\text{average } J_{45}) + 2(\text{average } J_{46}) \\ &= 19{\cdot}6 \text{ c/s,} \end{aligned}$$

in good agreement with the value of about 20 c/s obtained from the published spectrum.[7]

The analysis of α-proton signals for the determination of ΔG values will now be considered. It was shown earlier, that, for a mobile cyclohexane (I ⇌ II) which is substituted by an electron-attracting group X, and which is unsubstituted in the 2 and 6 positions, the calculated α-proton signal is a 1,2,1-triplet (separations J^*), each component being a triplet (separations J_{ae}). The method used to analyse the observed signal depends on the approximate value of x, which is usually obvious from the rough width of the signal, and on the values of J_{aa}, J_{ae} and J_{ee}, which are sometimes available by direct measurement of the α-proton signals of *cis*- and *trans*-4-t-butylcyclohexyl-X.

For small values of x, the α-proton signal will usually be unresolved, so that the analysis depends on the measurement of the band width at a particular fraction of the band height. The point at which the band width is best measured depends on the rough value of x, and on the value of J_{aa}, J_{ae} and J_{ee}; it can be determined from calculated spectra. For example, if J_{aa}, J_{ae} and J_{ee} are 11·5, 3·5 and 3·0 c/s respectively, the following relationships may be used:

$$\begin{aligned} &\text{for x between 0 and } \tfrac{1}{5}, && 2J^* + 2J_{ae} = \tfrac{1}{6}\text{-band width} \\ &\text{for x between } \tfrac{1}{5} \text{ and } \tfrac{1}{4}, && 2J^* + 2J_{ae} = \tfrac{1}{5}\text{-band width} \\ &\text{for x between } \tfrac{1}{4} \text{ and 1}, && 2J^* + 2J_{ae} = \tfrac{1}{4}\text{-band width} \end{aligned}$$

When x lies between $\frac{1}{4}$ and 1, the α-proton signal may be partly resolved. If, for example, lines 2 and 4 of a partly resolved quintet are clearly seen, the separation

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[10] H. Finegold and H. Kwart, *J. Org. Chem.* **27**, 2361 (1962).

2–4 may be equated to ($J^* + J_{ae}$). Also, if the outermost peaks of the signal are clearly observed, the separation between them can be equated to ($2J^* + 2J_{ae}$). A few examples will now be given.

The OH *group*

Cyclohexanol was dissolved in carbon tetrachloride and the solution was shaken with D_2O before the spectrum was determined. The $\frac{1}{4}$-band width of the α-proton signal was 24·0 ± 1 c/s (mean of 7 determinations: 23·5, 23·5, 23·7, 23·9, 24·1, 24·2 and 24·8 c/s). Thus $24{\cdot}0 \pm 1 = 2J^* + 2J_{ae}$. The coupling constants determined by Anet[2] were used, i.e. $J_{aa} = 11{\cdot}07$, J_{ae}(average) $= 3{\cdot}65$, $J_{ee} = 2{\cdot}72$ c/s. Calculation then gives x as 0·67 ± 0·06, the conformational equilibrium constant K as 2·17 ± 0·58 and ΔG (20°) as −0·43 ± 0·17 Kcal/mole^{-1}.

The NH_2 *group*

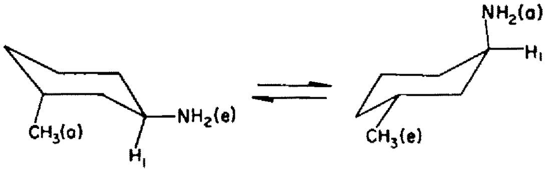
(a) *Calculation of* J_{aa}, J_{ae} *and* J_{ee}. The α-proton signal of *trans*-4-t-butylcyclohexylamine was not completely resolved. However, the corresponding signal, at $\tau = 7{\cdot}55$, of *cis*-3-methylcyclohexylamine in benzene, was resolved into eight of the nine lines expected on the basis of a conformationally homogeneous molecule. Direct measurement gave J_{aa} as 10·6 and J_{ae} as 3·2 c/s. The α-proton signal, at $\tau = 6{\cdot}90$, of *cis*-4-t-butylcyclohexylamine was unresolved. The $\frac{1}{6}$-band width ($= 2J_{ae} + 2J_{ee}$) was 11·0 ± 0·5 c/s; the $\frac{2}{3}$-band width ($= J_{ae} + J_{ee}$) was 5·75 ± 0·25 c/s. Taking the mean, J_{ee} is calculated to be 2·18 ± 0·25 c/s.

(b) *Spectrum of cyclohexylamine.* The α-proton signal for cyclohexylamine, dissolved in benzene, was unaffected when the sample was deuterated by being shaken with D_2O. The signal was largely unresolved, but the outermost peaks were seen reasonably clearly. The distance between these peaks was 24·4 ± 1 c/s (mean of 5 determinations: 23·8, 23·9, 24·0, 24·7 and 25·4 c/s).
Thus

$$24{\cdot}1 \pm 1 = 2J^* + 2J_{ae}$$

whence x is 0·81 ± 0·11, K is 7·44 ± 5·13 and ΔG (20°) is −1·0 ± 0·5 Kcal/mole^{-1}.

(c) *Spectrum of* trans-3-*methylcyclohexylamine.* In the NMR spectrum of the neat liquid, and of a solution in benzene, the α-proton (H_1) resonance appeared as a quintet, with spacings of between 3·8 and 4·4 c/s.



V
x

VI
1−x

The signal was resolved best in the spectrum of the neat liquid, lines 2, 3 and 4 being well-resolved. The separation between lines 2 and 4 was 8·1 ± 0·2 c/s. This can be equated to $J^* + J_{ae}$, whence calculation gives x as 0·325 ± 0·063 and K as 0·495 ± 0·140. The conformation (VI), with NH_2 axial, is thus in preponderance. Calculation gives ΔG for the conversion V → VI as $-0{\cdot}44 \pm 0{\cdot}18$ Kcal/mole^{-1}. If $\Delta G(\mathrm{Me})$ is taken as $-1{\cdot}7$ Kcal/mole^{-1} (cf.[11]), then $\Delta G(\mathrm{NH_2}, 20°)$ is $-1{\cdot}26 \pm 0{\cdot}18$ Kcal/mole^{-1}.

The Br group

The NMR spectrum of a solution of bromocyclohexane in carbon tetrachloride was determined. The α-proton signal was resolved into 7 peaks. The distance between extreme peaks of the signal was $23{\cdot}9 \pm 1$ c/s (mean of 5 determinations: 23·1, 23·57, 23·81, 24·15 and 24·75 c/s.

Thus

$$23{\cdot}9 \pm 1 = 2J^* + 2J_{ae}.$$

Using Lemieux and Lown's figures[6] for J_{aa}, J_{ae} and J_{ee}, calculation gives x as $0{\cdot}761 \pm 0{\cdot}061$, K as $3{\cdot}48 \pm 1{\cdot}15$ and ΔG (20°) as $-0{\cdot}70 \pm 0{\cdot}20$ Kcal/mole^{-1}.

Spectra were determined on an A.E.I. Spectrometer R.S.II. operating at 60 Mc/s.

[11] E. L. Eliel, E. W. Della and T. H. Williams, *Tetrahedron Letters* 831 (1963).