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PROTON MAGNETIC RESONANCE STUDIES OF CYCLIC COMPOUNDS—IV*

THE INFLUENCE OF ALKYL SUBSTITUENTS ON THE CHEMICAL SHIFTS OF THE RING PROTONS IN CYCLOHEXANE COMPOUNDS

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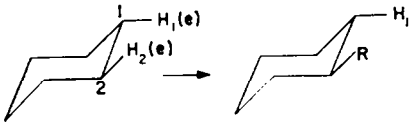
Abstract—The effects of alkyl substituents on the chemical shifts of ring protons in cyclohexane compounds are summarized. Application of these effects leads to a satisfactory explanation of a number of general spectral features, including the variation in broadness of the resonance signal observed for ring protons in *cis* and *trans* disubstituted cyclohexanes, and in *cis* and *trans* fused bicyclic systems.

BHACCA and Williams[1] have summarized the shielding and deshielding effects on ring protons in cyclohexane compounds caused by the replacement of hydrogen by the groups OH, OAc, SH and SAc. The effects produced when a hydrogen is replaced by an alkyl group are summarized below:

(a) *Conversion of* I *to* II, i.e. replacement of the equatorial hydrogen at position 2 by an alkyl group, causes a shielding of the equatorial hydrogen H_1. For R = Me, a shift of +0·28 ppm (+ ≡ shielding) has been recorded[2] for the α-proton of cyclohexanols. The published figures for 2-alkylcyclohexylamines[3] and for the neomenthols[4] suggest that the magnitude of the shielding is in the order Me (+0·4) ≫ Et, n-Pr, n-Bu (+0·2) > iso-Pr, cyclohexyl (+0·0) > t-Bu (−0·2). The effect for t-Bu is one of deshielding.



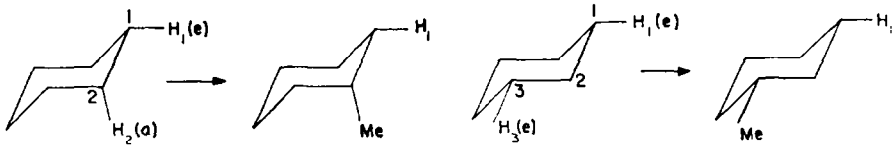
I II

(b) *Conversion of* III *to* IV, i.e. replacement of the axial hydrogen at position 2 by a methyl group, causes a shielding of the equatorial hydrogen H_1. A shift of +0·40 ppm has been reported for the α-proton of cyclohexanols.[2]

(c) *Conversion of* V *to* VI, i.e. replacement of the equatorial hydrogen at position 3 by a methyl group has a negligible effect on the equatorial hydrogen H_1. A shift of +0·01 ppm has been reported for the α-proton of cyclohexanols.[2]

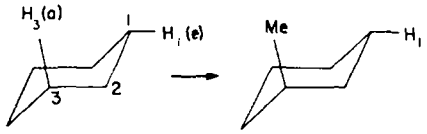
* Part III, H. Booth and G. C. Gidley, *Tetrahedron* **21**, 3429 (1965).

[1] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* p. 183. Holden-Day, San Francisco (1964).
[2] E. L. Eliel, M. H. Gianni and T. H. Williams, *Tetrahedron Letters* 741 (1962).
[3] H. Booth, N. C. Franklin and G. C. Gidley, *Tetrahedron* **21**, 1077 (1965).
[4] H. Feltkamp and N. C. Franklin, *Tetrahedron* **21**, 1541 (1965).



III IV V VI

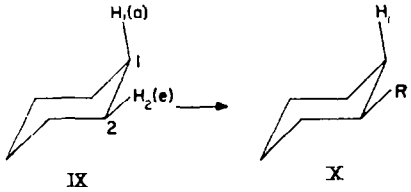
(d) *Conversion of* VII *to* VIII, i.e. replacement of the axial hydrogen at position 3 by a methyl group, causes a deshielding of the equatorial hydrogen H_1. A shift of 0·08 ppm has been reported for the α-proton of cyclohexanols.[2]



VII VIII

In agreement, the difference in chemical shift between the α-proton of *cis* 2-t-butylcyclohexanol[2] ($\tau = 5{\cdot}84$) and the α-proton of neoiso-t-butylmenthol[4] ($\tau = 5{\cdot}77$) is 0·07 ppm.

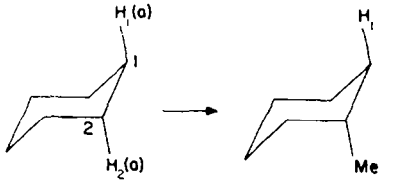
(e) *Conversion of* IX *to* X, i.e. replacement of the equatorial hydrogen at position 2 by an alkyl group causes a shielding of the axial hydrogen H_1. For the α-proton of



IX X

cyclohexanols, shifts of +0·47, +0·35, +0·18 and +0·03 have been reported[2] for R = Me, Et, iso-Pr and t-Bu respectively. For the α-proton of cyclohexylamines, a shift of ~ +0·4 occurs when R = Me.[5] For the α-proton of phthalimidocyclohexanes,[3] shifts of +0·44, +0·19, +0·01 and −0·13 occur when R = Me, Et(n-Pr, n-Bu), cyclohexyl and t-Bu respectively.

(f) *Conversion of* XI *to* XII, i.e. replacement of the axial hydrogen at position 2 by a methyl group causes a deshielding of the axial hydrogen H_1. Shifts of 0·19 and 0·20 ppm have been reported for the α-protons of cyclohexanols[2] and phthalimido-

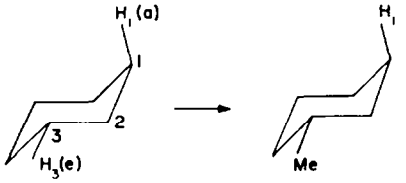


XI XII

[5] H. Feltkamp, N. C. Franklin, K. D. Thomas and W. Brugel, *Liebigs Ann.* **683**, 64 (1965).

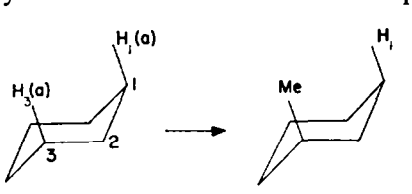
cyclohexanes[3] respectively. For the α-proton of substituted phthalimidocyclohexanes, the shifts for the alkyl groups Et, n-Pr and n-Bu are little different from that for the methyl group.

(g) *Conversion of* XIII *to* XIV, i.e. replacement of the equatorial hydrogen at position 3 by a methyl group causes a deshielding of the axial hydrogen H_1. A shift of 0·03 ppm has been recorded[2] for the α-proton of cyclohexanols.



XIII XIV

(h) *Conversion of* XV *to* XVI, i.e. replacement of the axial hydrogen at position 3 by a methyl group causes a deshielding of the axial hydrogen H_1. A value of 0·18 ppm has been reported[2] for cyclohexanols and a value of 0·25 ppm is recorded[6] for a



XV XVI

similar effect in *trans* quinolizidines. However, there is a much larger chemical shift difference between the α-proton resonances of *trans* 2-t-butylcyclohexanol[2] ($\tau = 6{\cdot}65$) and iso-t-butylmenthol[4] ($\tau = 6{\cdot}20$). A value of 0·2 ppm will be used here.

It is clear from the effects summarized above that estimations of conformational equilibria based on the use of chemical shifts may show considerable errors. At the same time many effects which were puzzling when first noted are now explained satisfactorily. These are now considered:

(A) *Ring proton signals in disubstituted cyclohexanes*

The τ values of the equatorial and axial protons of cyclohexane may be taken as 8·35 and 8·83 respectively.[7] Now the most significant effects produced by an equatorial methyl group are to cause a shielding of both adjacent equatorial protons (+0·28) and adjacent axial protons (+0·47). It is therefore understandable that *trans* 1,2-dimethylcyclohexane, which is largely confined to a diequatorial conformation, gives a temperature-independent spectrum in which a broad resonance is observed for the ring protons.[7,8] The most significant effects of an axial methyl group are a shielding (about +0·4) of the adjacent equatorial protons, and a deshielding (about −0·2) of four of the five axial protons. Clearly, the introduction of an axial methyl group will

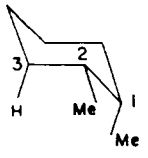
[6] F. Bohlmann, D. Schumann and H. Schulz, *Tetrahedron Letters* 173 (1965); H. P. Hamlow, S. Okuda and N. Nakagawa, *Ibid.* 2553 (1964).

[7] N. Muller and W. C. Tosch, *J. Chem. Phys.* **37**, 1167 (1962).

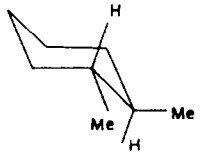
[8] S. Brownstein and R. Miller, *J. Org. Chem.* **24**, 1886 (1959).

cause the ring proton resonance to become sharper, an effect first observed by Brownstein and Miller,[8] and Musher,[9] but attributed entirely to rapid interconversion of conformations; the effect was later generalized by Muller and Tosch.[7] Moreover, the phenomenon is not confined to *alkyl* groups in an axial situation, since effects (b) and (f) also apply to other groups, e.g. OH and OAc.[1] This explains the "axial effect" of Feltkamp and Franklin.[5,10] For *cis* 1,2-dimethylcyclohexane (XVII) in which one methyl group is equatorial and the other axial, calculations based on effects (a) to (h) give the chemical shifts (τ values) of the 5 equatorial protons as 8·63, 8·76, 8·27, 8·36 and 8·55; and the chemical shifts of the 5 axial protons as 8·64, 8·61, 8·63, 8·80 and 9·10. In these calculations, it is assumed that substitution of methyl for hydrogen has a negligible effect on the chemical shift of a proton attached to the *same* carbon atom. In the case of equatorial methyl, the assumption is supported by a comparison of the published[11] chemical shift data for 2-methylpiperidine (2-axial proton at $\tau = 7{\cdot}43 \pm 0{\cdot}1$) with those for 3-methylpiperidine (6-axial proton at $\tau = 7{\cdot}48$) and for 4-methylpiperidine (2-axial protons at $\tau = 7{\cdot}40$). In the case of axial methyl, however, the assumption cannot be tested owing to lack of chemical shift data for appropriate compounds. It is expected, therefore, that a *conformationally rigid cis* 1,2-dimethylcyclohexane will show a relatively narrow band for the ring proton resonance, and this is indeed observed[7] in the low-temperature spectrum. A similar effect is expected, and observed,[7] for *cis* 1,4- and *trans* 1,3-dimethylcyclohexanes. At room temperature, the ring proton signals for these compounds become even sharper, as rapid interconversion between *equivalent* conformations causes the average chemical shift of the equatorial $\rightleftharpoons$ axial protons and the axial $\rightleftharpoons$ equatorial protons to become identical. However, it is now clear that the existence of a sharp signal at room temperature cannot in this case give any information on the rate of conformational inversion (cf.[9]). It is predicted that *cis* 1-t-butyl-4-methylcyclohexane, a molecule which is conformationally rigid even at room temperature, should show a fairly narrow ring proton resonance, and this, too, has been observed.[7]

(B) *Methyl proton signals in disubstituted cyclohexanes*



XVII

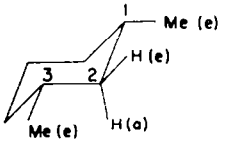


XVIII

As a result of effect (e), the axial methine protons in *trans* 1,2-dimethylcyclohexane (XVIII) are expected to have a chemical shift of about ($8{\cdot}83 + 0{\cdot}4 =$) $9{\cdot}23\ \tau$ i.e. similar to that of the methyl protons. This explains why the signal due to the methyl protons appears as an unresolved singlet.[7–9] The remaining dimethylcyclohexanes show the expected doublets for the methyl protons.

[9] J. I. Musher, *Spectrochim. Acta* **16**, 835 (1960).
[10] H. Feltkamp, N. C. Franklin, W. Kraus and W. Brugel, *Liebigs Ann.* **683**, 75 (1965).
[11] Varian Associates, *High Resolution NMR Spectra Catalogue* Vol. 2 (1963).

(C) *High field signals in* cis 1,3-*disubstituted cyclohexanes*



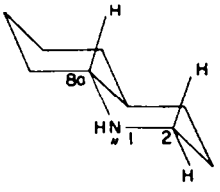
XIX

In *cis* 1,3-dimethylcyclohexane (XIX) the axial proton at position 2 is expected to have a chemical shift of about [8·83 + 2(0·4) =] 9·63 τ, and the observation[7] of signals well above the methyl doublet in this compound, and in *cis* 1,1,3,5-tetramethylcyclohexane is therefore understandable. For the same reason, the PMR spectrum[12] of *cis* (but not *trans*) 3-methylcyclohexylamine shows signals, due to the axial proton at position 2, which are to high field of the methyl doublet.

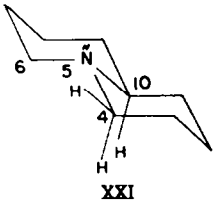
(D) *Compounds containing* trans *and* cis *fused cyclohexane rings*

trans Fused bicyclic systems, e.g. *trans* decalin, may be regarded as cyclohexanes substituted on adjacent atoms by two equatorial alkyl substituents, the substituent being —CH_2R. The shielding and deshielding effects of the rigid "substituent" —CH_2R are not known precisely, but they are expected to be similar to those of freely rotating —CH_3R, e.g. —CH_2CH_3. Therefore the broad resonance observed[13,14] is expected. However, the presence of axial substituents would have two important effects: (i) the number of axial protons is reduced, and (ii) the remaining axial protons are deshielded [effects (f) and (h)]. Both effects will lead to a narrower ring proton envelope and this has been observed[10] for *trans* decalin-1,4-diols with axial hydroxyl groups.

Effect (e) is also important for *trans* fused cyclohexane compounds since it leads to an unexpectedly high τ value for the protons in angular positions. For example, in the spectrum of *trans*-decahydroquinoline (XX) the two signals at low field (at τ = 7·1 and 7·5) are due to the equatorial and axial protons, respectively, at position 2; the 8a proton gives a signal at higher field (>8·0 τ).[12] Likewise, in quinolizidine (XXI), the axial proton at position 10 gives a signal with a τ value of ⩾8·2, whilst the low-field signals at 7·2 τ and 8·0 τ are due to the equatorial and axial protons respectively at position 4 (and the equivalent position 6).[6]



XX

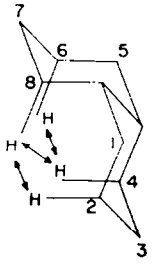


XXI

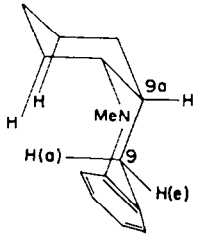
A *cis* fused bicyclic system, e.g. *cis* decalin (XXII), may be considered as a cyclohexane substituted on adjacent carbon atoms by one equatorial "substituent" —CH_2R

[12] H. Booth, unpublished observations.
[13] J. I. Musher and R. E. Richards, *Proc. Chem. Soc.* 230 (1958).
[14] W. B. Moniz and J. A. Dixon, *J. Amer. Chem. Soc.* **83**, 1671 (1961).

and one axial "substituent" —CH_2R. Therefore the previously discussed effects which lead to a relatively narrow ring proton resonance for *cis* 1,2-dimethylcyclohexane will also operate for *cis* decalin.



XXII



XXIII

Thus, for example, there is a mutual deshielding of the axial protons at positions 6 and 8 by the axial proton at position 4 [effect (h)]. In *cis* 1,2-dimethylcyclohexane (XVII), the axial proton at position 3 is shielded by the equatorial methyl at position 2, but in *cis* decalin (XXII), the corresponding effect on the axial proton at position 8 is offset by a deshielding, additional to the one mentioned above, due to the axial proton at position 2. The importance of these deshielding effects on axial protons subject to Van der Waals compression forces is illustrated by the case of *cis* octahydro-N-methylacridine (XXIII), where the resonance of the *quasi*-axial proton at position 9 was found[15] at lower field than that of the *quasi*-equatorial proton at position 9, despite the adjacent aromatic ring, of which any ring current effect would tend to selectively deshield the *quasi*-equatorial proton.

From the above, *cis* decalin is expected to give a relatively narrow resonance, even when conformationally rigid. As originally suggested by Muller and Tosch,[7] the spectrum of *cis* decalin at −120° is probably that of a single conformation, and the narrowness of the resonance observed[14] is in agreement with the treatment outlined above. At room temperature, the resonance is sharpened still further,[13,14] owing now to rapid interconversion of *equivalent* conformations. (cf. *cis* 1,2-dimethylcyclohexane). Previously, Moniz and Dixon[14] had suggested that *cis* decalin was still undergoing rapid conformational inversion even at −120°, but the results of Muller and Tosch led them to oppose this view. Harris and Sheppard[16] and, more recently, Riddell and Robinson,[17] suggested that the equatorial and axial protons in *cis* decalin have similar chemical shifts, a suggestion which is strongly supported by the arguments presented here.

Acknowledgement—I am grateful to Dr. J. Feeney, of Varian Associates Limited, for determining the spectrum of *trans* decahydroquinoline at 100 Mc/s.

[15] H. Booth, *Tetrahedron* **19**, 91 (1963); D. A. Archer, H. Booth, P. C. Crisp and J. Parrick, *J. Chem. Soc.* 330 (1963).
[16] R. K. Harris and N. Sheppard, *Proc. Chem. Soc.* 418 (1961).
[17] F. G. Riddell and M. J. T. Robinson, *Proc. Chem. Soc.* 227 (1965).